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Zika Virus: A Brief Overview

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Abstract

Zika Virus (ZIKV) belongs to *Flaviviridae* family and transmitted through mosquitoes (*Aedes* genus). The virus is enveloped, positive sense, non-segmented RNA genome. The genome consists of seven non-structural and three structural proteins. The symptoms of ZIKV infection are muscle pain, joint pain, headache, pain behind the eyes and conjunctivitis. Infection during pregnancy might cause microcephaly in new born. Recently there were ZIKV outbreaks in several parts across the globe. Diagnosis of ZIKV is mainly conducted by RT-PCR and MAC-ELISA. The review is focused in highlighting few important aspects about its outbreak, pathogenesis, diagnosis and control.

Keywords: Zika virus; *Aedes* genus; Transmission; Disease

Introduction

In 1947, scientists investigated yellow fever has been noted to rhesus macaque in a cage in the Zika Forest, near the East African Virus Research Institute in Entebbe, Uganda. The monkey developed fever and researchers isolated its serum and first described as Zika Virus (ZIKV). The virus was subsequently isolated from human in Nigeria in 1954 as a part of the outbreak in 1952. From its discovery until 2007, Zika virus infection from Africa and Southeast Asia were rare. In 2007, major epidemic occurred in Yap Island, Micronesia. Recently, it has been eminent that epidemics occurred in Polynesia, Easter Island, the Cook Islands and New Caledonia. Recent outbreak of Zika virus has occurred outside Africa and Asia confirmed in April 2015, in Brazil [1].

ZIKV belongs to the family *Flaviviridae*, an arthropod borne disease spreads through *Aedes aegypty* and *Aedes albopictus*. The virus was first isolated in the forest of Uganda at 1947 in rhesus monkeys through a monitoring network of sylvatic yellow fever and nomenclature as Zika. It was first identified in humans in 1952 in Uganda and the United Republic of Tanzania. ZIKV outbreaks have been recorded in Africa, the Americas, Asia and the Pacific. The incubation period is still not clear but symptoms remain last for 2-7 days. Despite growing knowledge about this virus, questions remain regarding the virus's vectors and reservoirs, pathogenesis, genetic diversity, and potential synergistic effects of co-infection with other circulating viruses. These questions highlight the need for research to optimize surveillance, patient management, and public health intervention in the current Zika virus epidemic.

Epidemiology

The ZIKV was first isolated from *Aedes africanus* in 1948 and it was detected, mainly in sylvatic, *Aedes* genus mosquitoes, including *Aedes furcifer*, luteocephalus, vitattus and. Apicoargenteus but in numerous countries ZIKV has been isolated from the antropophilic *Aedes* aegypti mosquitoes [1-4].

Serosurveillance data showed geographic distribution of human infection, including Egypt, East Africa, Nigeria, India, Thailand, Vietnam, the Philippines, and Malaysia [5-9]. In 1953, first human case of ZIKV was found in Nigeria [7]. In 2007, outbreak on several islands in the State of Yap, Federated States of Micronesia, resulted in an estimated 5000 infections among the total population of 6700 [8]. Recently ZIKV was indentified in Americas in March 2015 after an outbreak of exanthematous illness occurred in Brazil [10-12]. In 2013 and 2014, an outbreak in French Polynesia affected about 1% of the population [13]. In January 2016, ~ 150 cases of human infection by ZIKV were diagnosed in Martinique Island by the health agency.

Genome of ZIKV

ZIKV has a ~11 kb positive strand RNA genome which is composed of a single open reading frame, 10,794 pb in length, flanked by two non-coding regions [14]. The genome encodes three structural envelope (E), membrane precursor (prM) and capsid (C) and seven non structural (NS1, NS2A, NS2B, NS3, NS4A, NS4B and NS5) proteins [15]. The virion has an icosahedral capsid enclosed by a lipid envelope with a diameter of 40–70 nm. ZIKV multiplication occurs in the cytoplasm and, like other flaviviruses, its association with cellular organelles might exist to facilitate immune evasion and propagation [16].

Transmission of Zika Virus

Transmission of virus occurs through the bite of an infected mosquito from the *Aedes* genus, mainly *Aedes* aegypti in tropical regions. This is the same mosquito that transmits dengue, chikungunya and yellow fever. However, sexual transmission of Zika virus is also possible. Other modes of transmission such as blood transfusion and perinatal transmission are currently being investigated. *Aedes* mosquitoes are distributed globally, and native habitats of most species are warm tropical and subtropical regions [17-19]. Mosquito acquisition of the virus likely occurs during a blood meal; after uptake, the virus replicates and is transmitted to a reservoir animal at the next blood meal [20]. *Aedes albopictus* does not yet appear to be a major vector of ZIKV. However, its role in the 2007 Gabon outbreak, its wide distribution throughout the United States, and Zika virus's lack of restriction to a specific *Aedes* sp. indicate that this species could serve as a vector [9].

ZIKV disease outbreaks were reported for the first time from the Pacific in 2007 and 2013 and in 2015 from America and Africa. In total, 64 countries and territories have reported transmission of

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ZIKV since 1 January 2007. The viral diagnosis can be possible by laboratory testing for the presence of ZIKV RNA in the blood or other body fluids, such as urine or saliva. Centers for Disease Control and Prevention (CDC) list out the affected areas of virus transmission: Aruba, Barbados, Bolivia, Bonaire, Brazil, Colombia, Commonwealth of Puerto Rico (US territory), Costa Rica, Cuba, Curacao, Dominica, Dominican Republic, Ecuador, El Salvador, French Guiana, Guadeloupe, Guatemala, Guyana, Haiti, Honduras, Jamaica, Martinique, Mexico, Nicaragua, Panama, Paraguay, Saint Martin, Saint Vincent and the Grenadines, Sint Maarten, Suriname, Trinidad and Tobago, US Virgin Islands, Venezuela, American Samoa, Fiji, Kosrae (Federated States of Micronesia), Marshall Islands, New Caledonia, Samoa, Tonga, and Cape Verde. Zika virus infection is one of the most notifiable diseases in United States.

The *Aedes* mosquito is widespread in the Region, given the climatic conditions, temperature, and humidity in tropical countries. The virus has also been isolated in semen, and one case of possible person-to-person sexual transmission has been described [21]. Zika can be transmitted through blood, but this is an infrequent mechanism. The usual recommendations for safe transfusions should be followed. Earlier, ZIKV was mainly confined in Africa with some sporadic outbreaks in Asia. In May 2015, the public health authorities of Brazil confirmed the transmission of ZIKV in the northeast of the country. Since October 2015, it has spread to 21 countries and territories of the Americas. ZIKV spreads to people through mosquito bites. The virus was recovered from mosquitoes of *Aedes* genus including *Aedes africanus, Aedes apicoargenteus, Aedes leuteocephalus, Aedes aegypti, Aedes vitattus* and *Aedes furcifer*. Some reports suggest that Zika virus can also be transmitted to humans through blood transfusion, perinatal transmission and sexual transmission. However these modes are very rare. The virus was found on one occasion in semen. The disease cycle continues as reservoir host to mosquito to reservoir host; 2-5 days viremia in host, 5-7 days in mosquito, then back to the host.

The first association between ZIKV infection and neurological disorders occurred during the 2013–2014 ZIKV outbreaks in French Polynesia, which was associated with a 20-fold increase in cases of Guillain-Barre´ Syndrome (GBS) [22]. GBS is a post-infection autoimmune peripheral neuropathy that can produce pain, weakness, and paralysis; although GBS usually is temporary, GBS-induced respiratory paralysis can be fatal. Vaccines and therapeutics are needed urgently to combat ZIKV, and testing would be expedited by animal models of the different manifestations of disease. Multiple monkey species in the Zika forest were found to be seropositive for ZIKV. In response to the ongoing epidemic, new ZIKV studies have been initiated in animals including rhesus macaques. To address this fundamental gap in knowledge, ZIKV infection and disease in wild type (WT) C57BL/6 mice, as well as a large panel of immune-deficient transgenic mice, using several strains of ZIKV including a contemporary clinical isolate. Whereas 4- to 6-week-old WT mice did not develop clinically apparent disease, mice lacking interferon a/b (IFN-a/b) signaling (i.e., Ifnar1_/_ or Irf3_/_ Irf5_/_ Irf7_/_ Triple Knockout [TKO] mice) succumbed to infection with different ZIKV strains. Viral burden analysis revealed that Ifnar1_/_ but not WT mice sustained high levels of ZIKV in all tissues tested, including serum, spleen, brain, spinal cord, and testes. Our studies establish a mouse model of ZIKV pathogenesis with contemporary and historical virus strains that will be valuable for evaluating candidate vaccines and therapeutics as well as understanding the basic biology of ZIKV infection and disease [23]. Zika Virus (ZIKV) infection in pregnant women causes intrauterine growth restriction, spontaneous abortion, and microcephaly. Here, we describe two mouse models of placental and fetal disease associated with in utero transmission of ZIKV. Female mice lacking type I interferon signaling (Ifnar1-/-) crossed to wild-type (WT) males produced heterozygous fetuses resembling the immune status of human fetuses. Maternal inoculation at embryonic day 6.5 (E6.5) or E7.5 resulted in fetal demise that was associated with ZIKV infection of the placenta and fetal brain. ZIKV identified within trophoblasts of the maternal and fetal placenta is consistent with a trans-placental infection route. Antibody blockade of Ifnar1 signaling in WT pregnant mice enhanced ZIKV trans-placental infection although it did not result in fetal death. These models will facilitate the study of ZIKV pathogenesis, in utero transmission, and testing of therapies and vaccines to prevent congenital malformations [24]. There are concerns that pregnant women who become infected with Zika virus can transmit the disease to their unborn babies, with potentially serious consequences. Reports from several countries, most notably Brazil, demonstrate an increase in severe fetal birth defects and poor pregnancy outcomes in babies whose mothers were infected with Zika virus while pregnant. On 14 April 2016 the United States' Centers for Disease Control and Prevention released a statement concluding that prenatal Zika virus infection is a cause of microcephaly and other serious brain anomalies in developing fetuses [25].

Symptoms and Incubation Period

Symptoms of ZIKV

Low-grade fever, arthralgia, notably of small joints of hands and feet, with possible swollen joints, myalgia, headache, retro-ocular headaches, conjunctivitis, cutaneous maculopapular rash. Zika virus infection cause mild. However, as ZIKV infection cause rash that could be confused with diseases such as measles or dengue. Diagnosis of ZIKV will be based on symptoms, travel history and exclusion of other diseases including measles, rubella and dengue. The incubation period is typically 3–12 days. There is no specific therapy for ZIKV infection and acute symptoms typically resolve within 4–7 days [25].

Diagnosis, Treatment, Prevention, and Control

Diagnoses of ZIKV infection are based on detection of ZIKV nucleic acid by RT-PCR and the detection of IgM antibodies by IgM-capture Enzyme-Linked Immunosorbent Assay (MAC-ELISA). ZIKV RNA was detected in serum approximately 10 weeks after infection in fetus of pregnant woman with congenital infection [26]. Another cohort study indicates, RT-PCR had higher sensitivity in saliva than in serum although samples from some patients were positive in serum but not saliva after the onset of illness [27]. Although, immunohistochemical testing have been useful in establishing Zika virus infection in tissues of fetal losses and full-term infants who died shortly after birth [28]. The viral diagnosis can be possible by laboratory testing for the presence of ZIKV RNA in the blood or other body fluids, such as urine or saliva.

Since no vaccine is available for ZIKV infections, thus, prevention and control measures center on avoiding mosquito bites, reducing sexual transmission, and controlling the mosquito vector could prevent infection. Effective methods of prevention that are focused on reducing infections among pregnant women include avoiding unnecessary travel to areas of ongoing ZIKV transmission, avoiding unprotected sexual contact with partners who are at risk for ZIKV infection and using mosquito repellent [29]. Vector-control approach combined with detection of illness and development of a rapid response that involves the community are recommended [30].

Conclusion

Recent ZIKV infections have emerged as global threat. Immediate intervention like screening of viral isolates by cellular and molecular approach is required to understand its biology, mode of action and will provide an eminent linkage to develop targeted therapeutics. Southeast Asia is a tropical region where many tropical diseases are endemic. A very high prevalence of dengue and chikungunya fever is seen in this area. The main reason is the abundance of mosquito vector (*Aedes* species) in this area. Of interest, the same vector is also able to transmit Zika virus, hence, it is no doubt that the ZIKV infection can be seen and might be the new big problem in this area. Southeast Asian countries might be the next hot foci of ZIKV outbreak.

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