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Review Article

Zika virus: An emerging challenge for obstetrics and gynecology

Jhe-Jhih Lin [a], Ting-Yu Chin [b], Chih-Ping Chen [d, e, f, g, h, i], Hong-Lin Chan [a, **], Tzong-Yuan Wu [b, c, *]

[a] Institute of Bioinformatics and Structural Biology, National Tsing Hua University, Hsinchu, Taiwan
[b] Department of Bioscience Technology, Chung Yuan Christian University, Chungli, Taiwan
[c] Department of Medical Research, China Medical University Hospital, China Medical University, Taichung, Taiwan
[d] Department of Obstetrics and Gynecology, Mackay Memorial Hospital, Taipei, Taiwan
[e] Department of Medical Research, Mackay Memorial Hospital, Taipei, Taiwan
[f] Department of Biotechnology, Asia University, Taichung, Taiwan
[g] School of Chinese Medicine, College of Chinese Medicine, China Medical University, Taichung, Taiwan
[h] Institute of Clinical and Community Health Nursing, National Yang-Ming University, Taipei, Taiwan
[i] Department of Obstetrics and Gynecology, School of Medicine, National Yang-Ming University, Taipei, Taiwan

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ABSTRACT

Microcephaly is a rare birth defect, however, the re-emerging mosquito and sexual transmitted *flavivirus*, Zika virus (ZIKV), had changed the situation and caused an urgent challenge for the obstetrics and gynecology. This review will brief summarize the epidemiology and virology of ZIKV. And compared the animal models that had developed for the ZIKV infections. These animal models will be benefit for the development of vaccines and anti-ZIKV drugs. Furthermore, the genes that are involved in the causation of microcephaly were also summarized. Finally, the Wnt signal is critical for the brain development as well as innate immune response. Based on previous literatures, we proposed that ZIKV-induced microcephaly might result from the influence of Wnt/β-catenin signaling pathway through the regulation of miRNA-34.

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Introduction

Microcephaly is a rare birth defect in which the baby's cranium with a significantly decrease in occipito-frontal head circumference (OFC) of greater than two standard deviations (SD) below the normative mean, whereas those at least three SD below the mean may be described as “severe microcephaly” [1]. Microcephaly is divided into primary microcephaly (apparent congenitally) and secondary microcephaly (develops postnatally) and can be genetic or acquired (caused by environmental factors) [2]. Microcephaly can cause seizures, delay in development, and impair motor function and learning abilities. According the World Health Organization (WHO), the etiology of microcephaly is complex and occurs to be affected by several factors, including: (1) genetic abnormalities; (2) severe malnutrition during fetal life; (3) exposure to toxic chemicals such as arsenic, mercury, and radiation; (4) infection in the womb with the STORCH (syphilis, toxoplasmosis, other infections, rubella, cytomegalovirus (CMV) and herpes simplex) group [3]. The incidence of neonatal microcephaly, as reported in birth defect registers world-wide, differs from 1.3 to 150/100,000 live births, depending upon the population type and the range of SD used to define microcephaly [1]. Although the incidence of microcephaly in general was low, however, the incidence of microcephaly has unusually risen 20-fold in Brazil since 2015 (nearly 3000 cases of microcephaly have been reported) [4]. Epidemiological studies have linked these microcephaly cases to an old, *Aedes* mosquito-transmitted *flavivirus*, Zika virus (ZIKV). This re-emerging ZIKV epidemic may change the once rare microcephaly to be a new challenge issue of obstetrics and gynecology. In this brief review, we will describe the epidemiology and virology of ZIKV and propose the possible molecular mechanism that ZIKV might “hijack” Wnt signaling pathway on the neural stem cells and specifically impair fetal brain development and lead to microcephaly.

* Corresponding author. Department of Bioscience Technology, Chung Yuan Christian University, Chungli, Taiwan. Fax: +866 3 2653599.
** Corresponding author. Fax: +886 3 5715934.
E-mail addresses: hlchan@life.nthu.edu.tw (H.-L. Chan), tywu@cycu.edu.tw (T.-Y. Wu).

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The ZIKV pandemic

Before 21 century, only sporadic cases of ZIKV infection in humans were reported. However, in 2007, ZIKV emerged outside of Asia and Africa and caused the first large outbreak on Yap Island in the Federated States of Micronesia [5]. Unfortunately, a larger epidemic in French Polynesia during 2013–2014 was followed. This ZIKV outbreak in French Polynesia (FP), an overseas country of the French Republic, was estimated about 32,000 persons (11.5% of the population) with Zika-like symptoms [6,7]. Subsequently, ZIKV spread to New Caledonia [8], Japan [9], Norway [10], Easter Island [11], and continental France [12]. Recently, the ZIKV "fire" also burns to the Americas.

In 2015, there was a burst of ZIKV infection in the Americas. Brazil is the most ZIKV hit country, with estimates of 440,000–1,300,000 suspected cases of ZIKV have been reported [13,14]. Since then, ZIKV has rapidly spread far and wide across 50 other countries and territories in the Americas, including the Mexico and United States (World Map of Areas with Risk of Zika, according to the Centers for Disease Control and Prevention (CDC)). The current ZIKV epidemic provides evidence that ZIKV infection may be associated with severe neurological complications, such as Guillain–Barre syndrome (GBS) in adults in FP [15] and microcephaly in fetuses in Brazil [16]. Although, in the early 1970s, Bell et al. had showed that intracerebral infections of newborn and 5-week-old Swiss Webster mice with ZIKV can result in astrocyte hypertrophy and damage to hippocampal pyramidal neurons [17]. Furthermore, electron microscopy revealed that virions were present in both neurons and astroglial cells and morphogenesis in the endoplasmic reticulum (ER). These results have documented that ZIKV can infect and replicate in nervous system of mice, similar to other arboviruses [17].

Zika virus virology

ZIKV is an arbovirus of the Flaviviridae family, which includes dengue virus (DENV), West Nile virus (WNV), yellow fever virus, and tick-borne encephalitis virus (TBEV) [18], and is transmitted to humans by *Aedes* mosquitoes [19]. It was first isolated in Uganda in 1947 from a Rhesus monkey (strain MR-766) [20] and later the first human-infected case was detected in Nigeria in 1954 [21]. Before the 2007 outbreak in Yap, ZIKV has only been found to commonly circulate in tropical regions of Africa and Asia [22]. During outbreaks, humans serve as primary hosts for ZIKV [23], and both urban and sylvatic viral transmission have been demonstrated [24,25]. Otherwise, epizootics of ZIKV in monkeys had also been documented [26], but it is unclear whether primates are the only reservoir in the transmission of ZIKV to humans. Intriguingly, an unexpected finding is that ZIKV can be transmitted by sexual activity had been documented in 2011 [27]. And this may imply that both mosquito bites and human sexual activity could play a role in the recent ZIKV outbreak.

Like other member of the Flaviviridae family, ZIKV is constituted by a single positive sense RNA genome (+ssRNA), which is initially translated into a single polyprotein. This polyprotein is then cleaved post-translationally into individual proteins via host and viral proteases [28]. Three structural proteins named capsid (C), membrane precursor (PrM), and envelope (E) form capsids and seven nonstructural (NS) proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B and NS5) are involved in both viral transcription and replication and also modulate the host antiviral response [29,30]. Among nonstructural proteins, the glycosylated NS1 exists in two major forms, one is a membrane-bound dimer (mNS1) involved in the viral replication, and the other is a secreted hexamer (sNS1) that functions in pathogenesis and immune evasion via interacting with immune components [31–34]. Furthermore, it can also serve as a biomarker for early detection of flavivirus infection [35]. The other six NS proteins, NS2A to NS5, are thought to be involved in the formation of a replication complex on the cytoplasmic side of the ER membrane [36]. Two major lineages of ZIKV had been revealed by phylogenetic analyses (genomic sequencing): one includes the African lineage come from the original 1947 Ugandan strain (MR-766) [37] and the Asian lineage which are confirmed to be responsible for current outbreak [38].

The common clinical manifestations of ZIKV infection resembles that of DENV and chikungunya virus (CHIKV) may include fever, headache, arthralgia, myalgia, and maculopapular rash [39]. For these complex of symptoms that also hampers clinical diagnosis. Although 80% of human ZIKV infections are asymptomatic or may not get sick at all [5]. However, cases of neurological manifestations and the GBS were reported in FP during the 2013–14 ZIKV outbreak [12]. GBS is a rare autoimmune disorder in which the body's immune system attacks the peripheral nerves [40]. Often, the first symptoms of this disorder are weakness and tingling sensations in legs [41]. The exact cause of GBS is unknown and a new paradox was added that why this neurological disorder can be caused by ZIKV infection. However, it is learned that GBS is frequently preceded by an infectious illness such as acute respiratory or gastrointestinal infection [42]. There were 42 cases of GBS occurring during ZIKV outbreak in FP was recorded [43]. The observation of GBS in ZIKV cases implied an increase in the potential clinical severity of the disease [44]. More bizzare is that the Brazil Health Ministry reported a dramatically increased number of neonatal microcephaly cases (approximately 20 times higher than previous years) in the northeast region of Brazil and concerned this unusual epidemic linked with ZIKV [16]. And after Brazil raised the alarm, health officials in FP also identified more than a dozen babies born with neural defects [4]. Based on these epidemic observations, an emerging issue to clarify is that: Does the ZIKV is the only pathogen that lead to neurological manifestations, especially the microcephaly?

Zika virus caused microcephaly in animals and human

As aforementioned, the unusual increased microcephaly cases in the "hot zone" of ZIKV in Brazil, which may imply that ZIKV is the pathogenic factor. Moreover, causality relationship between the ZIKV epidemic and microcephaly had been experimentally confirmed and mentioned in a clinical case.

A study was conducted to examine the effects of ZIKV infection in neurospheres and brain organoids that generated from human iPSC-derived neural stem cells. This *in vitro* model demonstrates that ZIKV directly infects the brain cells and impairs their viability and grows in human neurospheres and brain organoids. These results implied that ZIKV interferes neurogenesis during human brain development [45]. To further confirm the observations of ZIKV infection in an *in vitro* brain organoids model, the establishment of animal models is necessary and critical. And these animal models should also be benefit for the development of the anti-ZIKV drugs and vaccines. At present, two kind of murine models of ZIKV infection have been established and published, including adult models [46,47] and pregnancy models [48–50], are summarized in Table 1. Moreover, several non-human primate models to study ZIKV are also under way [51]. These studies provide solid evidences that ZIKV can replicate in the embryonic brain and cause severe fetal abnormalities, which is consistent with the reported Zika-related microcephaly cases during the 2015–2016 American outbreak [39].

To test whether ZIKV can infect the embryonic mouse brain, $ZIKV^{SZ01}$ (Asian ZIKV strain) were directly injected into one side of

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