Anatomy Physiology & Biochemistry
International Journal
ISSN: 2476-1400

Juniper Publishers
key to the Researchers

Mini Review
Volume 2 Issue 5 – June 2017
DOI: 10.19080/APBIJ.2017.02.555598

Anatomy Physiol Biochem Int J

Microcephaly in Zika Virus Infection

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Submission: May 31, 2017; **Published:** June 14, 2017

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Abstract

Zika virus is a flavivirus known to cause microcephaly during development. The mechanism underlying Zika virus-induced neuropathogenesis is still poorly understood. Recent studies have utilized the cutting edge cell culture and animal model technologies to elucidate factors contributing to Zika virus-associated microcephaly. While future work is needed, current studies have suggested three main factors that contribute to Zika virus pathology: viral lineage, host immunity, and pregnancy stages. This mini review will focus on some of the recent findings that advanced our knowledge in Zika virus-associated microcephaly.

Keywords: Zika virus; neural stem cells; microcephaly

Abbreviations: ZIKV: Zika Virus; NSC: Neural Stem Cells; CT: Computed Tomography; TPCR: Transcription-Polymerase Chain Reaction

Introduction

Zika virus (ZIKV) is a flavivirus transmitted by the Aedes aegypti and Aedes albopictus mosquitoes with recent outbreaks in the Americas, and 84 countries and territories reporting active ZIKV transmission [1-3]. One of the greatest concerns regarding ZIKV infection is the risk of microcephaly. Microcephaly is a neurodevelopmental disorder characterized by a head size less than 2 standard deviations below the mean typical head size [4]. Infants with microcephaly can have a range of problems such as developmental delays, seizures, vision and hearing loss, and difficulty feeding.

There are two primary lineages of ZIKV, African and Asian; however, to date, only strains of the Asian lineage are associated with microcephaly [1,5-9]. The causal link between microcephaly and ZIKV infection was confirmed in 2016, as well as the capability of ZIKV to be transmitted by mosquito bites, sexual contact and contact with other bodily fluids [10-13]. ZIKV has been detected in placental, amniotic fluid, and brain cells [10,13-15]. Additionally, there has been a significant increase in microcephaly in Brazil linked to the ZIKV outbreak.

The WHO declared ZIKV-associated microcephaly and other ZIKV-related neurological disorders to be a "public health emergency of international concern". An estimated 0.034% to 13.2% of infants born to pregnant infected mothers will develop microcephaly [4,13,15-18]. It remains unclear what factors determine the susceptibility to ZIKV-related neurological abnormalities, though it is hypothesized that different ZIKV strains, pregnancy stages, and individual differences impact the response to ZIKV infection [16,17,19-21].

In vitro studies regarding ZIKV contributions to microcephaly

A normal brain develops from neural stem cells (NSCs) and their differentiated neural cells;therefore,abnormal proliferation or differentiation of NSCs during early development may result in microcephaly [22]. Research using human NSCs *in vitro* and *in vivo* mouse models verifies that ZIKV infects NSCs and can cause dysregulated survival, cell death, and decreased neuronal differentiation [7,21,23-27]. Studiesusing an African lineage murine neuro-adapted ZIKV strain (MR766) demonstrated an efficient infection of ZIKV in neural progenitors that were induced from human skin fibroblasts, which resulted significant cell death and apoptosis [28,29].

These studies showed high rates of infectivity and cell death in their respective models. While these findings represent the pioneering work *in vitro* with ZIKV and stem cells,the viral strain utilized was not reflective of clinically circulating strains. MR766 is an African lineage strain of ZIKV and has been passaged *in vitro* numerous times [30]. As a result, there are some discrepancies between findings reported in studies using MR766 and clinical

data. Specifically, clinical findings show only a small percentage of neural cells infected with ZIKV, and even though there is a reduction in neural populations, there is not a large amount of cell death [13,16,31].

Another factor to note in studies using induced pluripotent stem cells is that these cells have been genetically manipulated and reprogrammed from mature cells into pluripotent cells. While it remains undetermined if this genetic manipulation may play a role in viral infectivity and subsequent cell behavior, it is important to note differences between these cells and primary fetal cells.

A study was recently conducted utilizing a ZIKV strain from an outbreak in Puerto Rico in 2015 (PRVABC59) to infect primary human fetal neural progenitors [32]. This study showed lower infectivity rates of ZIKV as well as lower levels of apoptosis compared to the studies using MR766. This study was more reflective of clinical findings, and demonstrated that different strains of ZIKV could yield variable results. To better understand why only a subset of infants develop microcephaly, we used an *in vitro* culture system ofprimary human fetal brain-derived NSCs from three individual donors [33], and evaluated the effects of a ZIKV strain isolated from a 2015 Mexican outbreak (Mex1-7) on NSC survival and differentiation. Mex1-7 decreased NSC proliferation in all three donor strains, and, similar to the study using PRVABC59, there was very little apoptosis [32]. Interestingly, Mex1-7, significantly reduced neurogenesis (a process generating neurons) in two of the three donor strains, whereas the third donor strain experienced no change in neurogenesis.

The two strains that had a reduction in neurogenesis came from donors that were 9- and 13-week old of gestation. The donor strain that experienced no reduction in neurogenesis was also 13-week old [33]. This is an important factor considering clinical reports indicate that the first trimester of pregnancy is the time when fetusesare most susceptible to detrimental effects of ZIKV infection [19]. The donor-dependent responses of human NSCs in this study raised interesting questions about individual vulnerability and resiliency factors. Specifically, our study showed that in the two susceptible donor strains, there were significant alterations in transcriptome, particularly with regards to innate immunity and neurogenesis [33]. This suggests that innate immunity may be a key regulator of ZIKV's neurological disruption.

Use of in vitro systems is a valuable asset for ZIKV studies. They provide a relatively easy and well controlled system for understanding mechanistic details of ZIKV infection and subsequent cellular pathologies [34-37]. Recently, *in vitro* studies have shown that previous exposure to Dengue virus may result in antibody-dependent enhancement of ZIKV symptoms [38-41]. Furthermore, they provide a platform for medium to high throughput screening of various drugs and therapeutics to combat ZIKV infection [42-49].

In vivo studies regarding ZIKV contributions to microcephaly

While in vitro systems are critically important for developing our understanding of key mechanistic details, in vivo studies are necessary for providing a more translational perspective regarding the development and systemic pathogenesis of ZIKV-associated microcephaly. In non-human primates, it has been shown that subcutaneous inoculation with ZIKV results in development of fetal brain lesions [50]. However, due to financial and ethical constraints of non-human primate studies, most work was conducted in rodent models.

It is known ZIKV directly infects NSCs of the fetus and impairs growth in mice [18,20,51,52]. Wu and colleagues showed that ZIKV can be vertically transmitted from mother to fetus and result in cortical development deficits [51]. This study was unique in that it used an Asian lineage ZIKV strain isolated from a patient during an acute phase of the infection, and was subsequently used to infect fetal mice. They found that ZIKV infection significantly reduced proliferative neural cortical progenitor cells and altered genes associated with microcephaly and cell cycle progression [51]. Another study conducted by Cugola used a Brazilian ZIKV strain to infect pregnant dams, and revealed that the pups displayed a variety of birth defects including brain malformations [53]. They also found that there was a significant upregulation in genes associated with autophagy and apoptosis, indicating that the developmentalabnormalities may be a result of dysregulated autophagy and increased cell death during development [53].

In 2016, Rossi and colleagues developed and characterized a novel murine model to study ZIKV infection [54]. This unique mouse model is deficient in interferon-alpha receptor and displays an age-dependent response to ZIKV infection. Additionally, this mouse model is shown to harbor virus in the testis, similar to humans, which may make this strain optimal in studying sexual transmission of ZIKV.The age-dependent response of this mouse may make it ideal for studying developmental deficits associated with ZIKV infection as well as screen various drugs at different stages of infection [54].

Clinical studies regarding ZIKV contributions to microcephaly

In addition to animal and cell culture models to elucidate the mechanism of ZIKV infection, clinical studies have made great strides in detection and characterization of ZIKV pathologies. A study by de Fatima Vasco Aragao and colleagues detailed computed tomography (CT) findings from 22 children with signs of ZIKV infection [55]. This study showed that 95% of children had cortical development malformations, and 91% had decreased brain volume [55]. Ventriculomegaly, or enlargement of the ventricles, was observed in all of the 8 children who also underwent MRI [55]. Another study by Strafela et al. reported similar findings from autopsy evaluation of a ZIKV-infected

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fetal brain approximately 33 weeks old [56]. Among signs of lissencephaly and pachgyria, ventriculomegaly and thinning of white matter was also present [56]. Despite the clear clinical signs associated with ZIKV infection during development, there reamin key barriers to early diagnosis. A recent manuscript by Kaushik and colleagues discusses the use of smart sensing techniques to monitor ZIKV infection progression during development [57]. Use of smart sensing techniques such as electrochemical biosensors increases availability and ease of efficient diagnosis, compared to the broadly used reverse transcription-polymerase chain reaction (TPCR) method of diagnosis [57].

Conclusion

Advances in cell culture and animal models are beginning to help us understand the mechanism of ZIKV-induced microcephaly, though much work is still needed [58]. It is apparent from current work that ZIKV causes decreased proliferation and neurogenic differentiation during fetal development.However, given the relatively low infectivity of circulating ZIKV strains, more work should be done to investigate how host determinants mediate the development of microcephaly.Future studies should begin to focus on individual vulnerability factors which may increase susceptibility to ZIKV-associated neurological deficits. In this regard, current literature suggests host immunity may be a promising target. Figure 1 outlines the current understanding of ZIKV infection progression and highlights the current areas being targeted to prevent ZIKV infection and associated neurological deficits (Figure 1). In conclusion,ZIKV continues to present a public health threat, and the associated risk of microcephaly warrants further investigation.

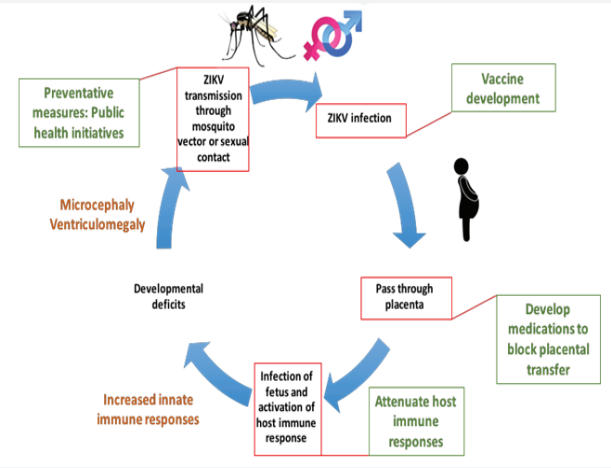

Figure 1: Schematic of ZIKV infection progression during development. The above diagram depicts the natural progression of ZIKV infection leading to developmental deficits such as microcephaly. The stages in red boxes are stages currently being targeted for prevention and treatment of ZIKV infection. Green boxes highlight the targets of research to prevent ZIKV-associated developmental deficits.

Conflict of Interest

The authors have no conflicts of interest to declare

Acknowledgement

E.L.M. drafted the manuscript and P.W. edited the manuscript. This work was supported by funds from the John S. Dunn Foundation (P.W.), R21AI129509- 01 (P.W. and N.V.), 4T32DA007287 (E.L.M.), and the Chief Research Office at the University of Texas Medical Branch (P.W.).

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