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Virology & Immunology Journal
ISSN: 2577-4379

Zika Virus Deregulate AKT signaling Pathway: Could be Reason of Microcephaly

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Editorial

Volume 2 Issue 8

Received Date: August 03, 2018

Published Date: August 14, 2018

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Editorial

Zika virus is a mosquito-borne flavivirus, has recently emerged as a serious global public health threat. ZIKV was first isolated in 1947 from a sentinel monkey in the Zika forest region of Uganda. The first human isolate was found in 1952, and its causal relationship to a mild dengue-like febrile illness was established in 1964 [1]. In the ensuing decades, rare and sporadic human cases with mild symptoms were recorded in Africa and South Asia; however, no significant epidemic was reported until 2007, when a large outbreak occurred in the Micronesian island of Yap [1]. In 2013, the virus caused outbreaks in several other Pacific islands including French Polynesia, Easter Island, the Cook Islands, and New Caledonia. Unusual neurological and autoimmune symptoms were noticed in some cases during these outbreaks, but no causal relationship with ZIKV was recognized. In early 2015, a ZIKV outbreak started across northeastern states of Brazil that soon spread throughout South America, and later to several other countries around the world including the United States. During this outbreak an unusual rise in cases of congenital neurological disorders such as microcephaly (MCPH) were reported in Brazil and other South American countries. This prompted intense investigations, and in April 2016 WHO announced a causal link between ZIKV and various congenital defects including microcephaly [1,2].

MCPH is a pediatric neurological disorder characterized by a smaller than normal head size in the affected babies. This is usually due to the underdevelopment of the fetal brain, especially of the cerebral cortex region. Depending on the severity of the condition, children with MCPH display a range of lifelong symptoms and disabilities including impaired cognitive development, delayed motor functions and speech, hyperactivity, facial distortions, difficulty with coordination and balance, loss of hearing, seizures, dwarfism or short stature, and other neurological abnormalities [1,2]. ZIKV is the latest addition to the many possible causes of MCPH that include genetic background, environmental factors, and other infectious agents [1]. There is ample evidence that upon infection of a pregnant mother, ZIKV can cross the placental barrier and infect fetal tissues, most notably the developing fetal brain [1-3]. Brain computed tomography (CT) scans of newborns with congenital Zika infection often show brain calcifications (mainly at the cortical-white matter junction), decreased brain volume with malformation of cerebral cortex, ventriculomegaly, hypoplasia of the cerebellum, and prominent protuberance of the occipital bone [3]. Studies in animal models have also provided evidence of transplacental transmission of ZIKV and subsequent infection of the fetus with signs of fetal neural abnormalities including cortical thinning, and MCPH (*Ahmad et al.,*2018; Li *et al.*, 2016). Research has shown that fetal neuronal and neural progenitor cells (NPS) are a major target of ZIKV [1,3]. Both *in vitro* and *in vivo* studies have indicated that the infected neuronal and NPS cells exhibit abnormal growth and differentiation, and they eventually die due to apoptosis [2]. Consistent with these observations, gene expression analyses have revealed dysregulation of genes that regulate DNA replication and

repair, cell cycle control, mitosis, cellular growth, and apoptosis [2,4]. Widespread apoptosis of neuronal and NPS cells in the ZIKV-infected fetal brain has been observed, and is believed to be a key reason for the depletion of neuronal cells resulting in cortical malformation and neurodegeneration [1,5]. Thus, apoptosis of neuronal and NPS cells appears to be an important factor in the pathogenesis of ZIKV-mediated MCPH. However, the exact molecular mechanism by which ZIKV causes apoptosis of infected cells is currently not clear.

Recently, Ling et al showed that ZIKV infection of NPCs leads to the suppression of AKT-mTOR pathway, and this results in activation of autophagy. The protein kinase B (AKT, also known as PKB) is an important cellular factor that not only plays a role in autophagy, but also positively regulates cell survival/proliferation, and antagonizes apoptosis. Transcriptome analyses of ZIKV-infected cells have also indicated transcriptional dysregulation of many AKT pathway genes conducive to apoptosis.

AKT is a relatively new member of the AGC kinase family. It was discovered in the early 1990s as a major regulator of the cell cycle [6]. Since then, over 30,000 papers have been published (~7000 in the past year) that show its major regulatory role in multiple aspects of cellular function. It has emerged as the focal point for many signal transduction pathways, regulating multiple cellular processes, such as glucose metabolism, transcription, apoptosis, cell proliferation, angiogenesis and cell motility [5,7]. Besides functioning as a kinase for many substrates involved in these processes, AKT forms complexes with other proteins that are not substrates, but rather act as modulators of its activity and function [7]. Besides, it has a basic role in regulating neuronal cell size and survival and is a critical survival factor that can modulate cellular pathways involved in apoptosis [7]. Over expression of AKT in cerebellar granule neurons prevents apoptosis during growth factor withdrawal [7]. However, expression of a dominant negative AKT or inhibition of PI3-K attenuates neuronal cell survival normally supported by growth factors [6,7]. Several studies have shown an important role for AKT for the survival of various neuronal cell types during cell injury. It promotes cell survival during free radical exposure in primary hippocampal neurons, neuronal cell lines and cerebral vascular endothelial cells [6].

AKT is recruited to the cell membrane by binding to lipids generated by PI3 kinase [2,6,7]. In response to ligand binding to plasma membrane receptors of different tyrosine kinases, PI3K generates phosphatidylinositol 3, 4, 5 trisphosphate (PIP3) at the cell surface, which leads to recruitment of AKT to the plasma membrane through its association with the newly generated PIP3 [6,7]. It is subsequently activated by phosphorylation at Thr-308, catalyzed by PDK1. A second phosphorylation at Ser-473, by an unknown kinase, can augment its activity up to 10-folds [2,7]. Activated AKT phosphorylates a number of other molecules including the clinically relevant target GSK3. GSK3 plays several roles in glucose metabolism, differentiation and development, intra cellular trafficking, apoptosis and regulation of gene transcription. In the brain, some studies suggest that GSK3, like AKT, could modulate synaptic plasticity.

Over the past decade, Bim has emerged as an essential pro-apoptotic protein for initiating the intrinsic apoptotic pathway under many physiological and pathophysiological conditions. The complex network regulating its expression and activity has made it possible to manipulate cell death at several nodal points. A fine balance in the intracellular expression levels of Bim and its regulatory proteins is crucial for properly regulating apoptosis. It has been reported that Bimis involved in the regulation of apoptosis in many different types of cells [8,9]. The apoptotic activity of Bim was thought to be mediated through several possible mechanisms [9]. The forkhead box transcription factor, class O (FoxO), is a mammalian homolog of DAF-16, which is known to regulate cellular apoptosis [8,9]. The FoxO factors including FoxO1, FoxO3a, FoxO4, and FoxO6 share DNA-binding specificity to a core consensus site called the forkhead-responsive element and regulate the transcription of genes involved in several cellular processes such as cell cycle arrest, apoptosis, and DNA repair in response to oxidative stress, differentiation, or glucose metabolism [3,9,10]. Among the FoxO members, FoxO3 activity is negatively regulated by PI3-K/Akt, which phosphorylates FoxO3 at multiple sites and forces FoxO3 into the cytoplasm, and thus, decreases its transcriptional activity [9,11,12]. Previously, cell death induced by FoxO3a was reported to be mediated through Bim, which is one of the FoxO-target genes [9].

In this study we explored ZIKV-induced mechanism of apoptosis in human neuronal cells (SH-SY5Y), primary embryonic rat neurons (PERNs) and one-week-old A129 mice. As a result, we found that Bim plays a pivotal role in ZIKV-induced intrinsic apoptosis and that FoxO3 is required for Bimactivation. These two proteins are positively regulated as a consequence of AKT being negatively regulated by ZIKV infection. Importantly, in this study we also identified differentially expressed micro-RNAs (miRs) in response to infection with ZIKV,

which are consistent with the critical role of AKT pathway during ZIKV infection.

Our preliminary data indicated that ZIKV induces apoptosis of neuronal cells through activation of the mitochondria-dependent intrinsic pathway. Using three different model systems, including an *in vivo* model, we provide evidence that a key factor in the ZIKV-induced apoptosis is the suppression of AKT in infected cells and could be possibly cause of microcephaly in the developing fetus. Therefore, this pathway offers potential targets for the treatment of ZIKV-induced neurological disorders.

Keywords: AKT; Neurodegeneration; Microcephaly; Apoptosis

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