

### ZIKV leads to Microcephaly

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#### COLUMN ARTICLE

“The current paradigm is that an important factor in ZIKV-induced Microcephaly(MCPH) is apoptosis of infected fetal cortical neural stem/ progenitor cells (NSCs) that results in depletion of neurons from the cortex and consequent malformation of the cerebral cortex leading to MCPH [1-4]”.

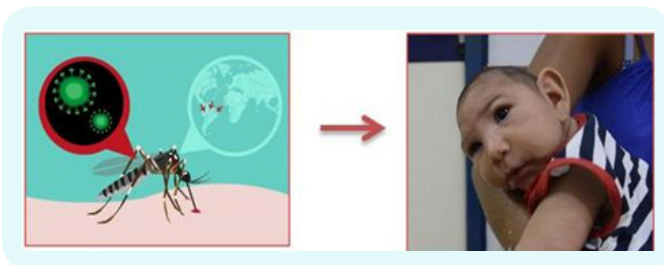
A human outbreak of Zika virus (ZIKV) that started in 2015 in Brazil has now spread to over 30 countries in the Americas with hundreds of thousands of confirmed or suspected cases. Nearly five hundred cases of travel-associated ZIKV infection have also been reported in the United States. ZIKV is primarily transmitted by mosquitos of the genus *Aedes* that are widely distributed throughout the world including much of the Southern United States. Additionally, the virus can also be transmitted from males to females by sexual contact. The epidemiological investigations during the current outbreak found a causal link between infection in pregnant women and development of microcephaly in their unborn babies. This finding is a cause for grave concern since microcephaly is a serious neural developmental disorder that can lead to significant postnatal developmental abnormalities and disabilities. Currently, it is not known how ZIKV causes microcephaly, but *in vitro* and *in vivo* data indicate that ZIKV causes apoptosis of fetal neural progenitor cells (NPCs) and/or cerebral neurons (CNs) that results in malformation of cerebral cortex leading to microcephaly

[5,6]. To have a deeper understanding of the pathogenesis of ZIKV-induced microcephaly, it is critical to decipher the molecular mechanisms by which ZIKV causes apoptosis of NPCs/CNs. In our preliminary investigations we observed that SH-SY5Y cells, which were derived from a human neuroblastoma line, also undergo apoptosis upon infection with ZIKV. Further investigations revealed that the level of host cell protein mTOR was dramatically reduced, phosphorylation of AKT was significantly diminished, and activity of FoxO3a transcription factor was upregulated in ZIKV-infected cells. These changes occurred within 24-48h post-infection and preceded any visible signs of apoptosis, which begin to manifest 3 days' post-infection. Both mTOR and AKT are critical components of a cell signaling pathway that promotes cell survival and growth, while FoxO3a, which is negatively regulated by AKT, causes transcriptional upregulation of genes involved in cellular apoptosis. These data suggested that a critical factor in ZIKV-induced apoptosis is inhibition of AKT-mTOR activity resulting in downregulation of the pro-survival/ growth pathway and upregulation FoxO3a-dependent pro-apoptotic pathway. We found that ZIKV causes apoptotic cell death of embryonic NPCs/CNs which may be the major factor microcephaly (Data not shown) [7-9].

#### Summary and Future Prospects

We have two separate aims will be carried out to investigate the role of AKT-mTOR pathway in ZIKV-induced apop-

tos. The first aim will be focused on obtaining evidence that ZIKV causes apoptosis by perturbing the AKT-mTOR pathway, and on identifying the components of the AKT-mTOR pathway that are dysregulated during ZIKV infection. The second aim will identify the ZIKV protein(s) that is directly responsible for dysregulation of the AKT-mTOR pathway and/or induction of apoptosis. It is important to note that while related, the two aims are not interdependent. Each will yield novel information independent of the other, but the combined efforts of the two aims will provide a detailed understanding of the ZIKV-induced apoptosis. The work here will identify the key viral and cellular factors that play role in the death of hNSCs, which represent a clinically relevant model. Importantly, our experimental design includes strategies to explore alternate mechanisms and effectors, should the experimental data do not support our original hypothesis. The studies here will provide new and useful information that will be used in our future studies and RO1 grant proposal(s), which will be centered around obtaining a direct connection between ZIKV-mediated dysregulation of AKT-mTOR pathway and MCPH, and subsequently on evaluating the identified viral and cellular factors as drug targets in a relevant animal model [10].



**Keywords:** Neural stem/progenitor cells (NSCs); Cerebral neurons (CNs); Zika virus (ZIKV); Microcephaly (MCPH)

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