Zika virus and brain defects in babies

Suan-Sin Foo, Weiqiang Chen, Qiming Liang, Jae Ung Jung*
Department of Molecular Microbiology and Immunology, Keck School of Medicine,
University of Southern California, Los Angeles, CA 90033, USA.
Mailing Address, jaeujung@med.usc.edu

The recent widespread outbreak of Zika virus (ZIKV) in the Americas and South East Asia is a major global health concern, largely due to the association with fetal abnormalities resulted from infection during pregnancy. The re-emerged Asian lineage ZIKV associated with fetal abnormalities appeared to have evolved from the original African lineage first discovered back in 1947 at Uganda. Despite a 90% sequence homology between the two lineages, stark differences in the replication kinetics, infectivity and immune responses have been reported during infection of neural cells. I will discuss two topics regarding ZIKV-mediated immune modulation and neuropathogenesis.

Blood monocytes are the frontline immunomodulators of the peripheral system categorized into classical or non-classical subsets, subsequently differentiating into M1 pro- or M2 anti-inflammatory macrophages upon stimulation. Pregnancy is a sophisticated immune-altering process which requires prudent immunomodulation of innate immunity to ensure healthy pregnancy outcome. In particular, circulating maternal monocytes play a crucial role, where the activation and transition of monocytes to macrophages is essential for healthy placental development. Using whole human blood infection, we identified that contrasting immunoprofiles of infected blood were a M1-skewed inflammation by African-lineage ZIKV infection and a M2-skewed immunotolerance by Asian-lineage ZIKV infection. Importantly, Asian-lineage ZIKV infection of pregnant women's blood drastically induced the M2-skewed immunotolerance of non-classical monocytes in conjunction with the aberrant expression of host genes associated with pregnancy complications. This study demonstrates the differential immunomodulatory responses of blood monocytes, particularly during pregnancy, upon infection with different lineages of ZIKV.

Among various key cellular pathways, Akt-mTOR signaling has been shown to be essential for brain development and autophagy regulation. We found that ZIKV infected human fetal neural stem cells (fNSCs), causing developmental defects and aberrant autophagy activation. Screens of the three structural proteins and seven nonstructural proteins of ZIKV identified that co-expression of the NS4A and NS4B not only inhibited the neurosphere growth and differentiation potential of fNSCs, but also induced autophagy for viral replication. Furthermore, the ZIKV NS4A-NS4B cooperatively suppressed the Akt-mTOR pathway, consequently linking their roles in neurogenesis suppression and autophagy induction. Our study demonstrates that the ZIKV NS4A and NS4B are potential virulence determinants of ZIKV pathogenesis, discovering the promising targets for anti-ZIKV therapeutic interventions.