Development of Model Systems to Study the Pathogenesis of Zika Virus-Mediated Eye Disease

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Zika virus (ZIKV) is a mosquito-borne flavivirus that causes microcephaly and congenital eye disease. Infected neonates develop eye malformations such as focal pigment mottling, chorioretinal atrophy, intraretinal hemorrhages, and blindness. The molecular mechanisms underlying the structural and developmental eye anomalies caused by ZIKV are not well understood. Our goal is to understand the mechanisms of ZIKV-mediated ocular cell injury. We utilized both in vitro cell-based and animal model systems to address this goal. We first evaluated the permissiveness of second-trimester human fetal retinal pigment epithelial (FRPE) cells to infection using the contemporary clinical isolate, ZIKV PRVABC59, circulating during the 2015-2016 outbreak in the Americas. We found that FRPEs were highly susceptible to ZIKV, resulting in apoptosis and reduced viability. Transcriptomics analysis of infected cells revealed the activation of inflammatory and VEGF signaling pathways, mitochondrial dysregulation, and altered cell survival signaling (PI3K/AKT). Induced pluripotent stem cell-derived retinal stem cells (iRSCs), a retinal stem cell population that is equivalent to the first-trimester of the developing eye, sustained lower levels of ZIKV replication compared with FRPE cells. We then wanted to investigate ZIKV disease pathogenesis using a type-I interferon receptor knockout (Ifnar1⁻/⁻) mouse model. Subcutaneous injection of ZIKV caused viremia, weight loss, and 100% mortality. RT-qPCR and immunocytochemistry showed the presence of ZIKV viral antigens in various cell layers of the retina and infiltration of macrophages and lymphocytes. Subsequently, we evaluated the pathogenesis of ZIKV ocular disease by direct viral inoculation on the eyes of mice. In this experimental condition, the infected animals did not show weight loss or neurological symptoms, however viremia was observed at 3 and 7 days post infection. Infected mice had enlarged spleens indicative of an active immune response. We further developed an ocular immunization platform against ZIKV using a mouse pregnancy model system. We found that ocular inoculation with ZIKV (single or double dose) protects pregnant mothers and their fetuses from subcutaneous challenge with ZIKV. We are currently investigating the molecular mechanisms of ZIKV-mediated congenital brain and eye disease.