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Novel approaches to study the Zika virus in the brain

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Zika virus (ZIKV) is a mosquito-transmitted flavivirus with a single-stranded RNA that was responsible for a major outbreak in the Americas in 2015, with 30,000 cases reported in Brazil by January 30th 2016 (1). Over the course of outbreak, Zika spread throughout the Americas, and infection during pregnancy has been linked to microcephaly and congenital abnormalities (2). This is caused by a particular tropism ZIKV exhibits to the central nervous system, impairing the development of the fetal brain, generating cerebral calcifications, ventriculomegaly, intrauterine growth restriction and in some cases, fetal demise. Congenital ZIKV infection was also linked to ocular abnormalities and blinding inflammatory disease in infants with or without reported microencephaly (3). Neurological manifestations were also reported in some adults, with most patients presenting Guillain-Barré syndrome, meningoencephalitis or transverse myelitis (4).

The substantial social and economic impact of ZIKV lead the World Health Organization to declare ZIKV a public health emergency of international concern (5). Animal models of human ZIKV are urgently needed to determine pathogenesis and long-term effects of the virus in the development of the infant brain, as well as to generate treatments and vaccines to prevent infection, particularly in pregnant women. Several murine models have been developed and although mice show growth restriction and brain infection (6, 7), substantial differences in CNS development limits the translational power of these findings. In contrast, nonhuman primates share many properties of neurological development with humans, and thus have emerged as a potentially powerful model to understand ZIKV pathology and to test candidate vaccines (8).

To establish a non-human primate (NHP) model of ZIKV infection, our group inoculated pregnant rhesus monkeys and their fetuses (*Macaca mulatta*) with a strain of ZIKV from Brazil in different gestational days to better understand developmental neuropathology in the fetal CNS (8). In order to reveal how the virus impacts the developing fetal brain, we used microscopy techniques such as high-resolution triple and quadruple immunofluorescence to study neuron and glial morphology and function.

The micrograph in this cover shows astrocytic processes surrounding a blood vessel in the CNS, forming the blood brain barrier (BBB), as well as the red blood cells inside the vessel

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in the infected fetal monkey brain. It is unclear how the ZIKV accesses the brain, but it is suggested that an increase in BBB permeability potentiates viral dissemination and replication in the CNS (9). One of our major goals has been to determine where ZIKV is present in the developing fetal brain, and then determine its impact on cellular development. We are also pursuing studies that we hope will elucidate the role of glial cells and neuroinflammation in the neuropathology caused by ZIKV infection. Together, we hope that these findings will shed light on fetal neuropathogenesis of ZIKV infection in a highly translational animal model of the disease that will ultimately allow us to test therapies and vaccines relevant for human health.

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