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CNS INFECTIONS

Mouse studies confirm the link between Zika virus infection and microcephaly

Epidemiological data from the current Zika virus (ZIKV) outbreak in Brazil have linked ZIKV infection in pregnancy with increased risk of microcephaly, but direct evidence for ZIKV-associated neurodevelopmental alterations has been absent. Now, two studies in mice show that the virus can infect the neural progenitor cells and neurons of the developing mouse fetus, resulting in signs of microcephaly.

"One of the most challenging problems in ZIKV research has been to develop an animal model for ZIKV pathogenesis," says Cheng-Feng Qin, who is based at the Beijing Institute of Microbiology and Epidemiology in China. Qin and Zhiheng Xu from the Institute of Genetics and Developmental Biology in Beijing injected Asian ZIKV strain SZ01 ($ZIKV^{SZ01}$) into the brains of unborn ICR mice. $ZIKV^{SZ01}$ replicated in the embryonic mouse brain, infected neural progenitor cells and destroyed neurons, thereby causing cortical thinning — a sign of microcephaly. Moreover, ZIKV infection suppressed proliferation and differentiation of neural progenitor cells

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The results, published in *Cell Stem Cell*, provide insight into the mechanisms via which ZIKV can impair neurodevelopment, and support a causal relationship between ZIKV infection and microcephaly. However, definitive proof that the virus could cross the placenta and enter the CNS of the developing fetus was still lacking.

In another study, published in *Nature*, Patrícia Beltrão-Braga and colleagues from the University of São Paulo, Brazil, injected the Brazilian ZIKV strain ($ZIKV^{BR}$) into pregnant SJL mice. Most mouse strains do not host ZIKV infection, but in these immunocompromised mice, $ZIKV^{BR}$ crossed the placenta and caused intrauterine growth restriction, which is also observed in some human newborns affected by the virus.

The findings are in line with a recent report, which described another ZIKV strain from the previous epidemic in French Polynesia to be capable of crossing the placenta in pregnant mice that had a genetically or pharmacologically impaired interferon response. According to this study, ZIKV caused placental damage and intrauterine growth restriction and/or fetal demise.

In line with the findings by Qin and Zu, Beltrão-Braga and co-workers report that histological assessment of the fetal mouse brains revealed cortical thinning in the offspring of SJL dams infected with $ZIKV^{BR}$. No alterations were detected in the offspring of pregnant SJL mice that were mock infected with yellow fever virus, which does not perturb neurodevelopment.

According to Beltrão-Braga, $ZIKV^{BR}$ infected many organs and tissues in the mouse fetuses; however, the amount of virus was particularly high in the CNS, indicating that ZIKV behaves in a neurotropic fashion. The researchers also discovered that, as reported by Xu and Qin, the virus was infecting cortical neural progenitor cells and, to a lesser extent, neurons. *In vitro*, ZIKV increases cell death in human cortical progenitor cells, and disrupts cell proliferation and cortical layer formation in human brain organoids, providing mechanistic insight into the neurodevelopmental perturbations associated with ZIKV infection in pregnancy.

The newly reported findings confirm the causal link between ZIKV infection in pregnancy and microcephaly. "On the basis of our findings and other evidence, we are now confident that ZIKV infection can result in microcephaly," Xu concludes.

Importantly, researchers can now use mouse models to test the effects of potential vaccines and therapies that could protect against ZIKV-associated neurodevelopmental deficits.

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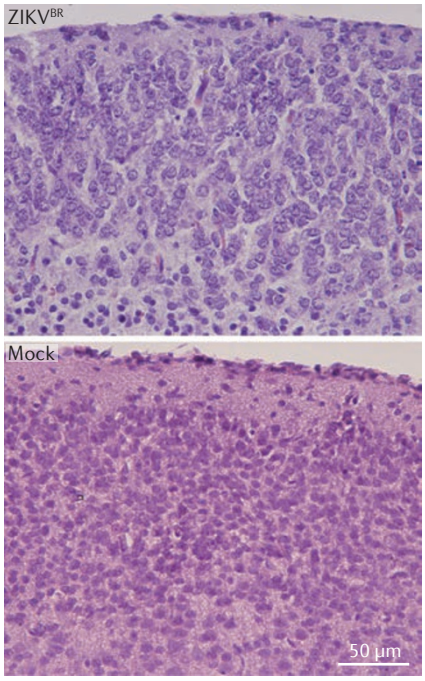

Histopathological analysis shows that mouse pups exposed to Brazilian Zika virus ($ZIKV^{BR}$) during fetal development show altered organization of the motor cortex compared with mock-infected pups (Mock). Image courtesy of P. Beltrão-Braga.

ORIGINAL ARTICLES Cugola, F. R. *et al.* The Brazilian Zika virus strain causes birth defects in experimental models. *Nature* http://dx.doi.org/10.1038/nature18296 (2016) | Li, C. N. *et al.* Zika virus disrupts neural progenitor development and leads to microcephaly in mice. *Cell Stem Cell* http://dx.doi.org/10.1016/j.stem.2016.04.017 (2016)

FURTHER READING Miner, J. J. *et al.* Zika virus infection during pregnancy in mice causes placental damage and fetal demise. *Cell* http://dx.doi.org/10.1016/j.cell.2016.05.008 (2016)