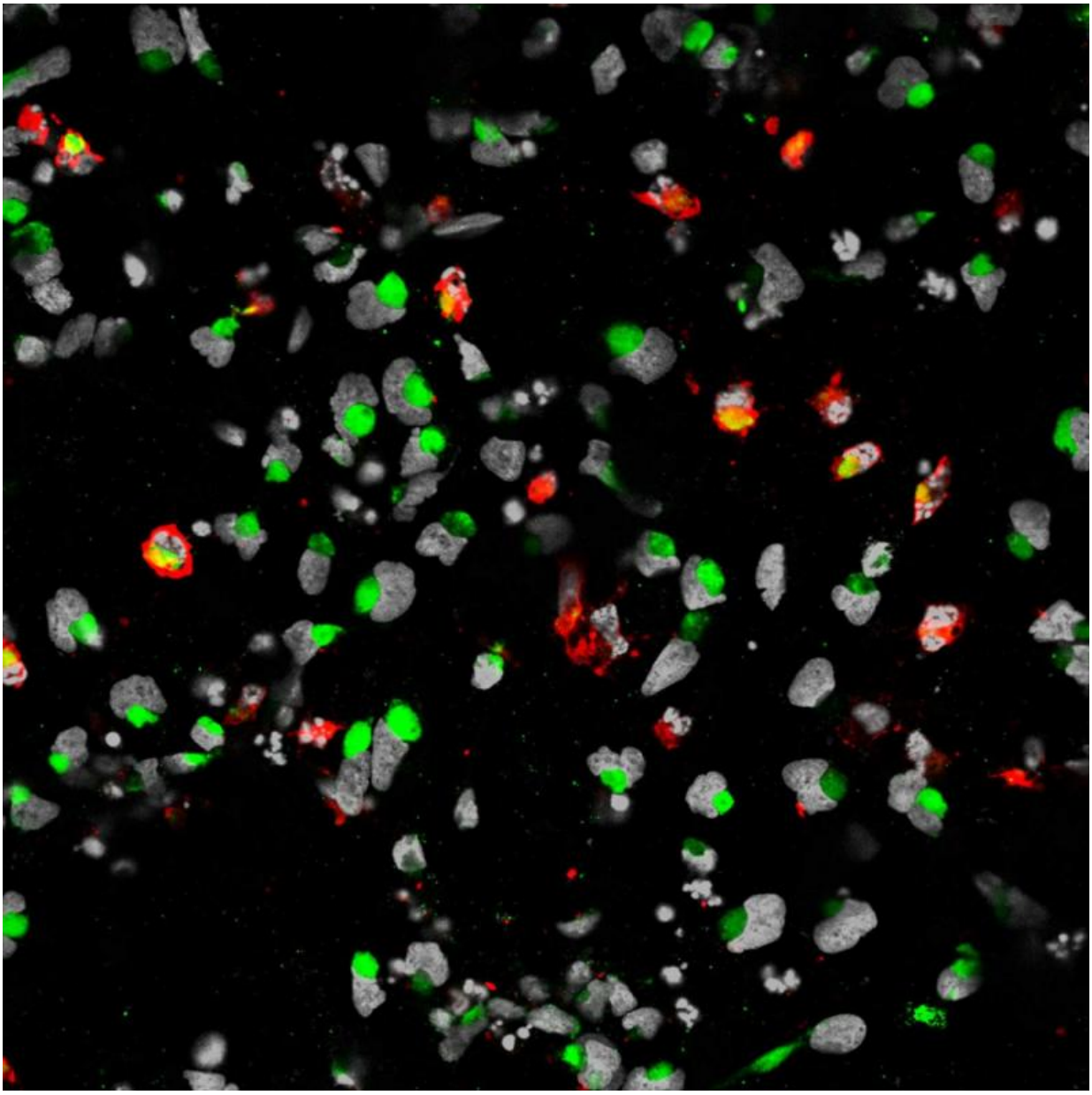
Zika virus infects human neural stem cells

March 4 2016



This image shows cell death of the human neural progenitor cells (hNPCs) is

mark by cleaved caspase 3 in red, the nuclei of hNPCs are labeled by DAPI in white/grey, and the ZIKA virus is labeled by ZIKA virus envelope protein in green. Credit: Sarah C. Ogden

The Zika virus infects a type of neural stem cell that gives rise to the brain's cerebral cortex, Johns Hopkins and Florida State researchers report March 4 in *Cell Stem Cell*. On laboratory dishes, these stem cells were found to be havens for viral reproduction, resulting in cell death and/or disruption of cell growth. While this study does not prove the direct link between Zika and microcephaly, it does pinpoint where the virus may be doing the most damage.

The researchers, led by Guo-li Ming and Hongjun Song of the Johns Hopkins University School of Medicine and Hengli Tang of Florida State University, with collaborators at the Emory University School of Medicine, worked around the clock for a month to conduct the study, which provides a new platform to learn about the Zika virus using neuronal cells derived from human induced pluripotent stem cells. In the near future, the researchers hope to grow mini-brains from the stem cells to observe the long-term effects of Zika infection on neural tissue and to screen for potential therapeutics.

"This is a first step, and there's a lot more that needs to be done," says Song, a neuroscientist and stem cell biologist. "What we show is that the Zika virus infects neuronal cells in dish that are counterparts to those that form the cortex during human brain development." We still don't know at all what is happening in the developing fetus. These findings may correlate with disrupted brain development, but direct evidence for a link between Zika virus and microcephaly is more likely to come from clinical studies, the researchers say.

As humans are typically infected by Zika virus carried by mosquitoes, the researchers also grew their Zika virus stock in mosquito cells for a few days before applying the virus onto the human cells used in all of their infection experiments.

One concerning discovery was that the stem cells that Zika was found to infect, called cortical neural precursors, become factories for viral replication. From a single infection, the virus particles spread through a plate of stem cells within a span of three days. There's also no evidence that the cells are employing antiviral responses, which means we don't know whether or how the virus is being cleared from the precursor cells.

"There are case reports for the Zika virus where they show that certain brain areas appear to have developed normally, but it is mostly the cortical structures that are missing," says Ming, a neuroscientist interested in brain disorders like microcephaly. "So a very important question that emerges from our work is whether the Zika virus specifically targets the neural progenitor mostly responsible for generating the cortex."

There are several other questions left to answer as well: why are the symptoms in adults so mild? How is the virus entering the nervous system of the developing fetus? Zika infects adults when mosquitoes deposit the virus on human skin, and our immune cells carry it into the blood. But how is the virus crossing the blood-brain barrier? And could Zika infect the small population of neural stem cells that adults keep above the brain stem in their hippocampus?

"We are trying to fill the knowledge gap between the infection and potential neurological defects," says first author Hengli Tang, the team's virologist whose lab studies RNA viruses like Zika, Dengue, and hepatitis C virus. "The questions we address here are among the very first questions people want to know the answers of."

Of note is how Ming, Song, Tang, and their collaborator Peng Jin, a geneticist at the Emory University School of Medicine, assembled a group of experts from four labs with different research interests to quickly tackle the Zika public health emergency. "We hope our results will help educate the public and government decision makers because they need to have more information on this virus, and we have to take it seriously," Song says.

More information: *Cell Stem Cell* (2016). DOI: 10.1016/j.stem.2016.02.016

Provided by Cell Press