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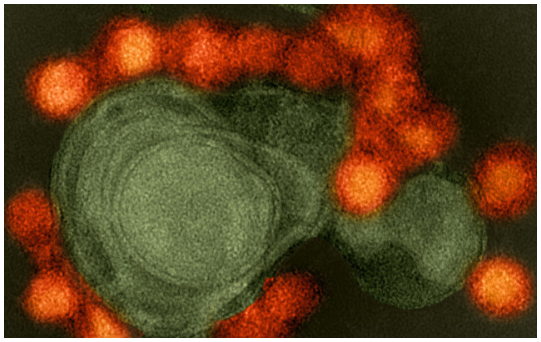
Zika Virus Targets and Kills Brain Cancer Stem Cells

In vitro and animal studies suggest virus that causes devastating neurological damage in developing fetuses might be new tool for improving survival rates in patients with glioblastomas

In developing fetuses, infection by the Zika virus can result in devastating neurological damage, most notably microcephaly and other brain malformations. In a new study, published today in *The Journal of Experimental Medicine*, researchers at the University of California San Diego School of Medicine and Washington University School of Medicine in St. Louis report the virus specifically targets and kills brain cancer stem cells.



Transmission electron microscope image of negative-stained, Fortaleza-strain Zika virus (red), isolated from a microcephaly case in Brazil. Image courtesy of NIAID.

The findings suggest the lethal power of the virus — notorious for causing infected babies to be born with under-sized, misshapen heads — could be directed at malignant cells in adult brains. Doing so might potentially improve survival rates for patients diagnosed with glioblastomas, the most common and aggressive form of brain cancer, with a median survival rate of just over 14 months after diagnosis.

“The Zika virus specifically targets neuroprogenitor cells in fetal and adult brains. Our research shows it also selectively targets and kills cancer stem cells, which tend to be resistant to standard treatments and a big reason why glioblastomas recur after surgery and result in shorter patient survival rates,” said Jeremy Rich, MD, professor of medicine at UC San Diego School of Medicine. Rich is co-senior author of the study with Michael S. Diamond, MD, PhD, professor, and Milan G. Chheda, MD, assistant professor, both at Washington University School of Medicine in St. Louis.

This year, more than 12,000 Americans will be diagnosed with glioblastomas, according to the American Brain Tumor Association. Among them: U.S. Senator John McCain, who announced his diagnosis in July. They are highly malignant. The two-year survival rate is 30 percent.

Standard treatment is aggressive: surgery, followed by chemotherapy and radiation. Yet most tumors recur within six months, fueled by a small population of glioblastoma stem cells that resist and survive treatment, continuing to divide and produce new tumor cells to replace those killed by cancer drugs.

For Zhe Zhu, MD, PhD, a postdoctoral scholar in Rich's lab and first author of the study, the hyper-reproductive capabilities of glioblastoma stem cells reminded him of neuroprogenitor cells, which fuel the explosive growth of developing brains. Zika virus specifically targets and kills neuroprogenitor cells.

So Zhu, with Rich, Diamond, Chheda and other collaborators, investigated whether the Zika virus might also target and kill cultured glioblastoma stem cells derived from patients being treated for the disease. They infected cultured tumors with one of two strains of the virus. Both strains spread through the tumors, infecting and killing stem cells while largely avoiding other tumor cells.

The findings, the authors said, suggest that chemotherapy-radiation treatment and a Zika infection appear to produce complementary results. Standard treatment kills most tumor cells but typically leaves stem cells intact. The Zika virus attacks stem cells but bypasses ordinary tumor cells.

"We see Zika one day being used in combination with current therapies to eradicate the whole tumor," said Chheda, an assistant professor of medicine and of neurology at Washington University School of Medicine.

To find out whether the virus could boost treatment efficacy in a live animal, researchers injected either the Zika virus or a saltwater placebo directly into glioblastoma tumors in 18 and 15 mice, respectively. Two weeks after injection, tumors were significantly smaller in the Zika-treated mice, who survived significantly longer than those given the placebo.

The scientists note that the idea of injecting a virus notorious for causing brain damage into patient's brains seems alarming, but they say Zika may prove a safe therapy with further testing because its primary target — neuroprogenitor cells — are rare in adult brains. The opposite is

true of fetal brains, which is part of the reason why a Zika infection before birth produces widespread and severe brain damage while a normal Zika infection in adults typically causes mild symptoms or none at all.

The researchers also conducted studies of the virus using brain tissue from epilepsy patients that showed the virus does not infect non-cancerous brain cells.

As an additional safety feature, the research team introduced two mutations that weakened the virus's ability to combat natural cellular defenses against infection, reasoning that while the mutated virus would still be able to grow in tumor cells, which have a poor anti-viral defense system, it would be quickly eliminated in healthy cells with a robust anti-viral response.

When they tested the mutated viral strain and the original parental strain in glioblastoma stem cells, they found that the original strain was more potent, but that the mutant strain also succeeded in killing the cancerous cells.

"We're going to introduce additional mutations to sensitize the virus even more to the innate immune response and prevent the infection from spreading," said Diamond, a professor of molecular microbiology, pathology and immunology. "Once we add a couple more, I think it's going to be impossible for the virus to overcome them and cause disease."

Co-authors of the study include: Matthew Gorman, Estefania Fernandez, Lisa McKenzie, Jiani Chai, Justin M. Richner, and Rong Zhang, Washington University, St. Louis; Christopher Hubert, and Briana Prager, Cleveland Clinic; Chao Shan, and Pei-Yong Shi, University of Texas Medical Branch; and Xiuxing Wang, UC San Diego.

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