New evidence links virus to brain cancer

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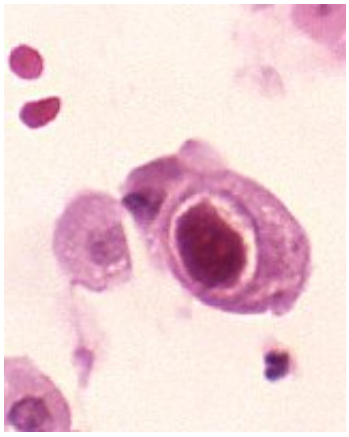

This photo shows an HCMV-infected cell.

(Medical Xpress) -- Tilting the scales in an ongoing debate, University of Wisconsin-Madison researchers have found new evidence that human cytomegalovirus (HCMV) is associated with glioblastoma multiforme (GBM), the brain cancer that killed Sen. Edward Kennedy.

The findings confirm what only a handful of scientists have found, but in a manner that University of Wisconsin School of Medicine and Public Health researchers believe enhances the scientific rigor of earlier studies.

The study, published in the advanced online edition (Nov. 16, 2011) of the *Journal of Virology*, hints for the first time that HCMV may work differently than other cancer-related viruses - possibly by affecting only tumor stem cells, self-renewing cells that keep the tumor growing.

The new research may place HCMV in an expanding group of viruses associated with cancer.

"As many as 15 to 20 percent of all human cancers are caused by viruses, and the number is growing," says HCMV expert Dr. Robert Kalejta, associate professor of oncology at the UW School of Medicine and Public Health (SMPH). "The viruses may not cause cancer on their own, but they play a critical role in the process."

Among others, human papilloma virus (HPV) causes cervical cancer, Epstein-Barr virus (EBV) causes lymphoma and hepatitis C virus (HCV) causes liver cancer.

HCMV's role in GBM has been debated, with many scientists and clinicians remaining skeptical. Oncologist Dr. Charles Cobbs of California Pacific Medical Center has been the main proponent of the theory that HCMV contributes to GBM.

Dr. John Kuo, assistant professor of neurological surgery and human oncology and a cancer stem cell scientist at the School of Medicine and Public Health, was one of the skeptical ones, but he says he's now convinced that HCMV is associated with human GBM specimens.

Still, the association does not prove a causal relationship between HCMV and the development of GBM, he says.

"This study may open up a new unexplored area of research for this incurable disease," says Kuo, who is director of the Comprehensive Brain Tumor Program at UW Hospital and Clinics. He also coordinates clinical trials as chair of the brain tumor group at the Carbone Cancer Center.

Kuo and colleagues on the UW brain tumor team currently treat GBM patients with the standard regimen of surgery, followed by radiation and chemotherapy. More research is needed before anti-viral drugs against HCMV could be considered for clinical trials, says Kuo, whose group contributed to the Journal of Virology paper.

Two years ago, Kalejta's team added support to Cobb's position when it showed that two HCMV proteins shut down a key protein that restricts tumor growth in general.

"HCMV can also do every one of the things that are

generally considered the 10 hallmarks of cancer," says Kalejta, a member of the McArdle Laboratory for Cancer Research, Carbone Cancer Center, Stem Cell and Regenerative Medicine Center and Institute for Molecular Virology at UW-Madison.

The problem with studying HCMV is that the virus is present in a harmless way in almost everyone, so scientists can't ask if HCMV-positive people are more likely to get cancer than people without HCMV.

Kalejta's postdoctoral fellow Dr. Padhma Ranganatan used a standard laboratory test, rather than the ultra-sensitive test Cobb has used, to see if HCMV was present in 75 GBM samples. The UW-Madison researchers also looked to see if the entire virus genome - all of its DNA - rather than just a portion of it was present in the tissues. Finally, they wanted to learn if all cells within the tumor or just some of them were infected.

The analysis showed that HCMV is statistically more likely to be present in GBM sample tissues than in other brain tumor and epileptic brain tissues. The whole virus genome, not a portion of it, was present in GBM samples. And the data suggested that a minority of GBM cells were infected with HCMV.

"We hypothesize that HCMV may be infecting only tumor stem cells, unlike other viruses, which infect every single tumor cell," says Kalejta. "This leads us to predict that HCMV functions by a unique mechanism that no other virus uses."

Kalejta hopes to begin looking for the new mechanism soon. If there is such a mechanism, it could open a new door in cancer biology. It would also convert many more people to the idea that HCMV plays a key role in GBM.

"But I think the tide is now turning on the debate," Kalejta says.

Provided by University of Wisconsin-Madison