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Cytomegalovirus might speed brain-cancer growth

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A virus that infects most Americans but that usually remains dormant in the body might speed the progression of an aggressive form of brain cancer when particular genes are shut off in tumor cells, new research shows. The animal study by researchers at the Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC – James) and at Dana Farber Cancer Institute suggests that cytomegalovirus (CMV) might significantly accelerate the development and progression of glioblastoma, a deadly form of brain cancer.

The virus by itself does not cause cancer, the study suggests, but it might influence tumor development when changes occur that silence two genes called p53 and Nf1 in tumor cells. These genes are protective "tumor suppressor" genes that normally cause cells to die before they become malignant. But cancer-related changes can silence them, enabling malignant cells to survive, multiply and form tumors.

The findings are published in the journal *Cancer Research*. Some 50 to 80 percent of Americans become infected with CMV by age 40. The virus is transmitted by contact with infected saliva and other body fluids, and through sexual contact. Most people are infected early in life and then the virus remains dormant.

"CMV has been detected in many cancer types, suggesting that it might be reactivated when cancer occurs in the body," says co-corresponding author and researcher Dr. Chang-Hyuk Kwon, assistant professor of

neurological surgery, at the OSUCCC – James and at the Dardinger Center for Neuro-oncology and Neurosciences.

The researchers also learned that CMV stimulates tumor-cell proliferation by activating a biochemical cell pathway called STAT3. In healthy cells, STAT3 plays an important role in controlling cell proliferation.

"Our data indicate that CMV contributes to glioblastoma when already-mutated cancer cells proliferate using the STAT3 signaling pathway," Kwon says. "We believe that CMV's action occurs in the tumor's cells of origin early in tumor initiation."

The findings raise questions about how cancer is studied, says co-corresponding author Dr. E. Antonio Chiocca, chairman of neurosurgery at the Brigham and Women's Hospital and surgical director for the Center for Neuro-oncology at Dana-Farber Cancer Institute in Boston.

"First, we usually study cancer in models that are virus-free, but our findings suggest that CMV might play a significant role in human cancers," he says.

"Secondly, anti-viral therapy against CMV might now be justified for human cancers, and immune responses to such cancer-modulating viruses should be carefully studied," Chiocca says.

About 18,500 new cases of glioblastoma multiforme are expected annually in the U.S., and 12,760 Americans are expected to die of the disease.

Kwon, Chiocca and their colleagues conducted the study using two mouse models infected with murine CMV (MCMV). One model developed glioblastoma spontaneously; the other received implants of

human glioblastoma cells. Key technical findings include:

- MCMV-infected mice with genetic mutations in p53 and NF1 in their brain cells that predisposed them to spontaneous glioblastoma had shorter survival than non-MCMV-infected mice with the same mutations;
- Implanting human gliomas into the brains of MCMV-infected animals significantly shortened their survival compared with controls;
- MCMV infection increased levels of activated STAT3 in neural stem cells, the cells in which glioblastoma is thought to originate;
- Human CMV increased STAT3 activation and proliferation of patient-derived glioblastoma cells; a STAT3 inhibitor reversed this effect in cell and animal models.

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