Patient's own immune cells may blunt viral therapy for brain cancer

25 November 2012

Doctors now use cancer-killing viruses to treat some patients with lethal, fast-growing brain tumors. Clinical trials show that these therapeutic viruses are safe but less effective than expected.

A new study led by researchers at the Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC – James) shows that the reason for this is in part due to the patient's own immune system, which quickly works to eliminate the anticancer virus.

The findings, published in the journal *Nature Medicine*, show that the body responds to the anticancer virus as it does to an infection. Within hours, specialized immune cells called natural killer (NK) cells move in to eliminate the therapeutic virus in the brain.

The researchers discovered that the NK cells attack the viruses when they express specific molecules on their surface called NKp30 and NKp46. "These receptor molecules enable the NK cells to recognize and destroy the anticancer viruses before the viruses can destroy the tumor," says co-senior author Dr. Michael A. Caligiuri, director of Ohio State's Comprehensive Cancer Center and CEO of the James Cancer Hospital and Solove Research Institute, and a senior author of the study.

"When we blocked those receptors, the virus has more time to work, and mice with these brain tumors live longer. The next step is to block these molecules on NK cells in glioblastoma patients and see if we can improve their outcome," says Caligiuri, who is also the John L. Marakas Nationwide Insurance Enterprise Foundation Chair in Cancer Research. This study of cancer-cell-killing, or oncolytic, viruses is an example of the value of translational research, in which a problem observed during clinical trials is studied in the laboratory to devise a solution.

"In this case, clinical trials of oncolytic viruses proved safe for use in the brain, but we noticed substantial numbers of immune cells in brain tumors after treatment," says senior author and neurosurgeon Dr. E. Antonio Chiocca, who was professor and chair of neurological surgery while at Ohio State University.

"To understand this process, we went back to the laboratory and showed that NK cells rapidly infiltrate tumors in mice that have been treated with the therapeutic virus. These NK cells also signal other inflammatory cells to come in and destroy the cancer-killing virus in the tumor."

The study used an oncolytic herpes simplex virus, human glioblastoma tumor tissue and mouse models, one of which hosted both human glioblastoma cells and human NK cells. Key technical findings include:

- Replication of the therapeutic virus in tumor cells in an animal model rapidly attracted subsets of NK cells to the tumor site;
- NK cells in tumors activated other immune cells (i.e., macrophages and microglia) that have both antiviral and anticancer properties;
- Depletion of NK cells improves the survival of tumor-bearing mice treated with the therapeutic virus;
- NK cells that destroy virus-infected tumor cells express the NKp30 and NKp46 receptors molecules that recognize the virus.

"Once we identify the molecules on glioblastoma cells that these NK cell receptors bind with, we might be able to use them to identify patients who will be sensitive to this therapy," Caligiuri says.

Provided by Ohio State University Medical Center