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Cancer-killing viruses influence tumor blood-vessel growth

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Viruses genetically designed to kill cancer cells offer a promising strategy for treating incurable brain tumors such as glioblastoma, but the body's natural defenses often eliminate the viruses before they can eliminate the tumor.

The findings of an animal study by researchers at the Ohio State University Comprehensive Cancer Center help explain why this happens and could improve this therapy for brain cancer patients.

The research, published in the June 10 issue of the journal *Molecular Therapy*, shows that as the viruses destroy the tumor cells, they cause the cells to make proteins that stimulate the growth of new blood vessels to the tumor. These vessels transport immune cells that eradicate the viruses and actually stimulate regrowth of the tumor.

"This study points to an important side effect of oncolytic viral therapy that may limit its efficacy," says principal investigator Balveen Kaur, a researcher with Ohio State's Comprehensive Cancer Center and the Dardinger Laboratory for Neuro-oncology and Neurosciences.

"Knowing this, we can now work on designing a combination therapy that will inhibit this effect and enhance the action of the viral therapy."

The researchers also discovered that, in infected tumor cells, the viruses changed the activity levels of three genes linked to blood-vessel growth in gliomas.

One of these genes, CYR61, was nine times more active in virus-treated tumor cells than in uninfected tumors. The researchers also showed that the higher the dose of virus used, the greater the gene's activity.

For this study, Kaur and her colleagues implanted human glioma cells into rodents with a working immune system, then injected the resulting tumors of some with a cancer-killing, or oncolytic, virus called hrR3. The treated animals lived 17 days compared with 14 days for the untreated controls. The virus-treated tumors had roughly five times more blood vessels in them than the untreated tumors.

Treated tumors also showed changes in gene activity for three of 11 genes thought to play a role in blood-vessel development in gliomas. Of these, CYR61 showing an 8.9-fold increase in activity 12 hours after treatment.

Last, the researchers verified the virus-caused increase in CYR61 gene activity using several different glioma cell lines and glioma cells from patients, and several strains of active, replicating oncolytic viruses.

"In all cases, we observed a rise in CYR61 gene activity, which indicates that this change in gene activity may represent a host response to the viral infection," Kaur says. Non-replicating viruses had no affect on the gene's activity.

Kaur and her colleagues are now studying why cells turn on this gene when infected with oncolytic viruses and whether the protein that results from this gene activation might serve as a biomarker reflecting patients' response to oncolytic virus therapy.

"Measuring a patient's response to viral infection is currently not feasible," Kaur says, "so if this were to work, it would be a significant advance."

Source: Ohio State University

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