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# Blood-vessel blocker aids cancer-killing virus

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Cancer-killing viruses are a promising therapy for incurable brain tumors, but their effectiveness has been limited in part because immune cells rapidly move in and eliminate them.

That immune response might be slowed, and the virus given more time to kill cancer cells, by blocking the growth of blood vessels in the tumor, new research here suggests.

The animal study indicates that pretreatment with an antiangiogenic agent – a drug that blocks blood-vessel growth – might improve the effectiveness of cancer-killing viruses.

The study, led by researchers at the Ohio State University Comprehensive Cancer Center, is published online in the *Journal of the National Cancer Institute* with an accompanying editorial.

“Our work suggest that antiangiogenic agents can reduce virus-induced inflammation in brain-tumor tissue and improve the antitumor efficacy of oncolytic virus therapy by lengthening the time it takes the immune system to clear the virus,” says principal investigator Balveen Kaur, assistant professor of neurological surgery.

“Much additional work is needed to validate these findings in other tumor models, but we hope that our findings will eventually be translated into clinical trials and one day help patients.”

Kaur and her colleagues set out to learn how a cancer-killing, or

oncolytic, virus affected the blood vessels in a brain-tumor model.

Kazuhiko Kurozumi, a visiting research scholar from Japan in Kaur's laboratory, first implanted rat glioma cells into the brains of several groups of rats. Seven days later, he injected a cancer-killing virus, called hrR3, into the growing tumors. This virus is a modified form of herpes simplex virus type 1 that reproduces and kills only tumor cells.

The virus caused the tumor blood vessels to become significantly more leaky compared with tumor blood vessels from control animals, and high numbers of white blood cells – immune cells – entered the tumor tissue.

The virus also triggered a twofold or greater change in the activity of 48 of 84 genes that are involved in inflammation and immune responses. Of those genes that were highly changed was the gene for interferon-gamma (IFNg), a substance important for coordinating immune responses to viral infections.

"Together, these findings indicate that the oncolytic virus triggered a local immune response in the tumor that would curtail its effectiveness," Kaur says.

In other rats, the researchers injected into developing tumors an agent that blocks blood-vessel growth. Four days after that, they injected the virus into the tumors. The agent is called cRGD (cyclic peptide of arginine-glycine-aspartic).

Tumors in animals that received the agent had significantly fewer blood vessels than control animals (28 vs. 62 per area of tumor), and the vessels were significantly less leaky. Also, fewer immune cells were drawn to the tumor from the bloodstream.

Furthermore, the treated animals showed a more than twofold drop in

the activity of 19 genes associated with inflammation, including the gene for IFNg.

Finally, animals pretreated with the blood-vessel-growth inhibitor lived an average of 21 days, while control animals that received only the virus lived 17 days.

“The agent increased survival by about 23 percent,” Kaur says, “which means a lot because these tumors are very aggressive.

Source: Ohio State University

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