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# Immune system may play key role in viral therapy's effectiveness against tumors

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Viral therapy for childhood cancer could possibly improve if treatments such as chemotherapy do not first suppress patients' immune systems, according to findings published today in the journal *Molecular Therapy—Oncolytics*. Research on mouse tumors resembling rhabdomyosarcoma, the most common soft tissue sarcoma in children, revealed that the immune system's T cells may be just as critical to fighting tumor cells as the viral therapy injections themselves.

The research team, led by senior author Timothy P. Cripe, MD, PhD, chief of the Division of Hematology/Oncology/BMT at Nationwide Children's Hospital, found that virotherapy doesn't always require a strong virus infection of cancer cells to cause tumors to shrink or die. Instead, the therapy may benefit from the activity of the immune system operating in tandem, creating a synergistic, cancer-killing effect. The work arose from the team's recognition of two challenges to viral therapy research.

"Most work done in this field has tested virotherapy in human tumors implanted into mice with defective immune systems," said Dr. Cripe, also a principal investigator in the Center for Childhood Cancer and Blood Diseases in The Research Institute. "If the only effect of the virus is to infect and kill the tumor cells, that should be fine. But if the immune system's T cells play a role, we wouldn't see their impact, since these mice don't have T cells."

The second challenge to researching viral therapies for childhood

cancers is the fact that mouse cells don't get infected with human viruses as easily as human cells. Clinician-scientists worried that studying mouse cells wouldn't be truly reflective of human disease. However, some human tumor cells may also be hard to infect with viral therapies, Dr. Cripe reasoned, and knowing how cells respond in those situations could also be important to improving cancer treatments.

Dr. Cripe and his colleagues at The Ohio State University, the University of Pittsburgh School of Medicine and Cincinnati Children's Hospital Medical Center tested how well the oncolytic viral therapy—a cancer-killing form of the herpes simplex virus, called oHSV—infected and killed tumor cells in mice with and without a healthy immune system.

"Despite the low infection levels of mouse cells with oHSV, we were able to cause a delay in tumor growth in one of the cancer models and even cure many of the mice in a second model," said first author Jennifer Leddon, who conducted much of the laboratory work during a research experience in the Center for Childhood Cancer and Blood Diseases. "Even a small amount of infection with oHSV appears to be enough to trigger an immune response to the tumor."

Much of the cancer-killing effect of the oHSV injections was lost when the researchers tested the therapy in tumors of mice with defective immune systems. These results indicate that in some cases, even limited infection of the tumor cells with the actual virotherapy could be sufficient to stimulate the immune system's T cells to attack the cancer on its own. According to Dr. Cripe, the study suggests that some patients could respond to therapy even if their tumors aren't very infectable by the virus, provided their immune systems were stimulated by the viral therapy to attack the tumor cells.

The work also provides food for thought regarding the delivery of clinical therapies. "Our data suggest that immunosuppression may not be

the best strategy to help virotherapy do its job," said Dr. Cripe, who was recently appointed as an associate editor of *Molecular Therapy—Oncolytics*. "In the past, we assumed a healthy immune system would fight off the virus infection before it could cause tumor shrinkage. But a healthy immune system might actually be helpful to virotherapy."

Many clinical trials combine virotherapy with chemotherapy or other immunosuppressive agents to try to allow the virus to survive and infect as many cancer cells as possible. Although changes in treatment methodology still have to be studied, Dr. Cripe believes it may be that the timing of various treatments is what matters, and that perhaps initially suppressing immunity could allow the virus to infect a large number of tumor cells before relieving the immunosuppression to allow the body's own T cells to fight off the tumor.

Despite these promising clinical implications, the team calls for additional research on the interplay between viral therapy, infectability and immune system response.

"The effective immune response didn't happen in every tumor model we tested, so we still need to figure out exactly what triggered the tumor shrinkage and how to predict which tumors will shrink in response to virotherapy," said Leddon, who is also working toward her medical and doctoral degrees at the University of Cincinnati.

The team also compared the animals' responses to the therapy's effects in laboratory cell samples and found that in vitro studies did not predict how well the viral therapy and immune response would fight tumor cells in vivo. This opens the door to further investigation of past potential therapies that may have been dismissed because of ineffectiveness in laboratory studies, causing researchers to presume the treatment would be equally ineffective in living cancer models.

"Most researchers have relied on cell lines to screen the effect of drugs and other treatments including viruses," said Dr. Cripe, who also is a professor at The Ohio State University College of Medicine. "Our work suggests relying on cell lines might cause researchers to miss effective therapies if they dismiss them based solely on cell line data."

Dr. Cripe and his collaborators plan to investigate which tumor cells respond well to oHSV infection and immune system response and whether targeting their ability to resist viral infection or T cell attacks could improve the viral therapy's effectiveness.

Provided by Nationwide Children's Hospital