Evidence supports blocking immune response to enhance viral therapy against solid tumors

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Following several years of study, investigators have found more evidence that viral therapy to treat solid tumors can be enhanced by blocking the body's natural immune response.

Oncolytic viruses have shown promise as anticancer agents, with variations of the herpes simplex virus (HSV) among the most commonly used. However, many studies have shown that the effectiveness of viral therapy to eradicate tumors has not been as successful with patients as it has been in the lab. These results have led researchers to examine the body's immune system response to determine what effect it may have toward decreasing the effectiveness of viral therapy.

A new study, published in the March 12, 2013 issue of *Molecular Therapy* and led by Timothy Cripe, MD, PhD, division chief of Hematology/Oncology and Bone Marrow Transplantation at Nationwide Children's Hospital, is shedding additional light on how viral therapy combined with a suppressed immune response could be more effective against solid tumors.

Dr. Cripe and a team of investigators studied the effects of vascular endothelial growth factor (VEGF), a substance commonly released during an immune, or pro-inflammatory, response to a viral infection. VEGF is responsible for angiogenesis, new blood vessel growth near an injured or infected site.

VEGF is also important for tumor growth, raising the possibility that its

response to virus infection might get in the way of viral therapy.

"We sought to determine if a pro-angiogenic response occurs during viral therapy for cancer, to what extent it may limit antitumor effectiveness, and if it could be counteracted by antiangiogenic therapy," explains Dr. Cripe, who is also a professor of Pediatrics at The Ohio State University College of Medicine.

Their research demonstrates that an anti-VEGF antibody markedly enhances the anti-tumor effect of an oncolytic virus (oHSV) injected into a tumor. They also discovered that the anti-tumor effect was due to both enhanced antiangiogenesis and the modulation of the tumor's immune response. However the effect was not due to the virus replicating within the tumor.

"One of the most important outcomes of this study is the strong rationale for developing a clinical trial combining the use of oHSV and the FDA-approved anti-VEGF product, bevacizumab," said Dr. Cripe. "Virus therapy or anti-VEGF therapy alone each independently prolonged survival of mouse models implanted with Ewing sarcoma, but all of those mice eventually succumbed to their cancer. In contrast, the combination of virus and anti-VEGF therapies cured 90 percent of the mice. Virus therapy is a very promising area of cancer treatment, and studies such as these will bring us even closer to success."

Future studies will be developed to determine if immune responses vary among tumor types and if targeted therapy for specific aspects of the immune response will be more effective than completely suppressing the immune system.

Provided by Nationwide Children's Hospital