Scientists use genetically altered virus to get tumors to tattle on themselves

May 11 2011

Scientists have used a genetically re-engineered herpes virus that selectively hunts down and infects cancerous tumors and then delivers genetic material that prompts cancers to secrete a biomarker and reveal their presence.

According to a study appearing May 11 in *PLoS (Public Library of Science) ONE*, the novel technology has the potential to vastly improve cancer diagnosis by allowing the disease to be caught at much earlier stages and to monitor the effectiveness of therapy.

Researchers at Cincinnati Children's Hospital Medical Center who conducted the study say the new technique – developed in preclinical mouse models – could also be more cost effective and portable than current scanning technologies. This would make it useful for diagnosing cancers in less developed parts of the world.

"Our study represents a proof-of-principle in mice, and there is certainly room for further refinement. If ultimately validated in human trials, it could have implications for people with known cancer risk or who have a history of cancer and high risk of recurrence," said Timothy Cripe, M.D., Ph.D., senior investigator on the study and a physician and researcher in the Division of Oncology at Cincinnati Children's.

"Early cancer detection is vital to improve cure rates because cancer stage predicts prognosis, but biomarkers are known for only a few cancer types. We were able to use a reprogrammed herpes virus

administered intravenously to deliver genetic information that induces a known blood biomarker for cancer to be secreted by cancer cells," explained Dr. Cripe, who collaborated on the study with first author, Andrew Browne, Ph.D., a fourth-year medical student at the University of Cincinnati (UC) College of Medicine and a recent graduate from UC's Department of Electrical and Computer Engineering.

The researchers engineered a herpes simplex virus mutant they called rQ-M38G, reprogramming its genetic makeup so it bypasses healthy tissues and instead targets rapidly dividing cancer cells for infection. They also genetically armed the virus so it prompts cancer cells to secrete Gaussia luciferase (GLuc).

GLuc is a luminescent, easily detectable protein the researchers used as a universal blood biomarker for cancer cells infected by rQ-M38G. Because rQ-M38G/GLuc might also help shrink cancer, it is part of a new class of agents dubbed "theragnostics" that can simultaneously be used for diagnosis and therapy, Dr. Cripe said.

Initially the researchers tested rQ-M38G on laboratory cell cultures of healthy dormant human skin cells and on rapidly dividing cancer cells. Virus replication and biomarker production were very low in the dormant normal cells. In contrast, virus replication and biomarker production were much higher in tumor cell lines of malignant peripheral nerve sheath tumors, osteosarcoma (bone cancer), rhabdomyosarcoma (muscle cancer) and Ewing sarcoma.

Researchers then tested the virus's detection capabilities in mouse models of these same cancers by injecting rQ-M38G into their tail veins, and for comparison into the tail veins of healthy control mice. Non-tumor bearing mice showed background signals for the virus without significant replications or biomarker production. More than 90 percent of the tumor bearing mice showed significant virus replication and

biomarker production.

The technology even worked in some mice with only microscopic amounts of cancer in their kidneys, researchers report. If it were to work as well in humans, the scientists estimate that hidden tumors less than half-inch in diameter might be detectable. Because of the anticipated immune response against the virus and the GLuc protein in humans, further refinements of the technology will likely be needed to be able to use it more than once.

The study is one more example of the expanding research into using reprogrammed HSV as novel methods to treat or diagnose cancer, especially as medicine reaches the limits of modern chemotherapies. Dr. Cripe said this creates an urgent need for new strategies against stubborn metastatic disease. Less than 30 percent of patients with metastatic cancer survive beyond five years, despite the aggressive use of modern combination therapies that include chemotherapy.

Provided by Cincinnati Children's Hospital Medical Center