Viruses kill pancreatic tumors in preclinical model

March 20 2012

(Medical Xpress) -- An intra-tumor injection of a virus prevented further growth of some pancreatic tumors and eradicated others in mouse models of pancreatic ductal adenocarcinoma. However, some tumors continued growing despite this treatment, proving resistant to the viruses. The research is published in the March Journal of Virology.

About 95 percent of pancreatic cancers are pancreatic ductal adenocarcinomas (PDAs). PDA is considered to be one of the most lethal malignancies, resulting in a five year survival rate of only 8-20 percent.

In this study, the researchers, led by Valery Z. Grdzelishvili of the University of North Carolina, Charlotte, tested several species of virus against pancreatic tumors, most notably vesicular stomatitis virus (VSV), a type of virus that is commonly used in the laboratory. Previous studies had demonstrated that some other viruses, including adenoviruses, herpesviruses, and reoviruses, could be used to kill pancreatic cancer cells in some animal models of pancreatic cancer.

VSV has several qualities which make it attractive as a potential oncolytic (cancer killing) agent. First, unlike some other viruses (including adenoviruses),VSV replication does not require the cancer cell to express a specific receptor in order to infect that cell, and therefore it can infect most any cancer cell. Second, replication occurs in the cytoplasm of host cells, which means that there is no risk that it will cause healthy host cells to become cancerous, says Grdzelishvili. Third,

this virus's genome is easily manipulated, which would make it fairly practical to adjust levels of foreign gene expression to enhance the virus' specificity for particular cancers, and its ability to kill them. Fourth, unlike with some other viruses, humans have no preexisting immunity to VSV.

In the study, the cancer-killing potential of several VSV variants was tested against 13 clinically relevant cell lines of PDA, including both primary PDA tumors and PDA metastases to the liver and lymph nodes, all derived from human patients, and compared these to adenoviruses, Sendai virus, and respiratory syncytial virus.

"In general, VSV variants showed superior oncolytic abilities compared to other viruses, and some cell lines that exhibited resistance to other viruses were successfully eradicated by VSV," says Grdzelishvili. "However, we found that PDA cells were surprisingly heterogeneous in their susceptibility to virus-induced oncolysis and several cell lines were resistant to all tested viruses." In producing and responding to interferon, many pancreatic cancers seemed to retain the normal antiviral responses that normal, healthy cells have towards viruses, he says.

Grdzelishvili emphasizes that the VSV's ability to kill cancer cells in mouse models by no means guarantees that it would perform similarly in cancer patients due to complex tumor microenvironments and compromised immune responses. Most animal models involve simply inserting human cancer cells underneath the animal's skin, so that the cancers and their environments are both quite different from cancer growing naturally in a human.

However, cancer cells that are resistant to virus in laboratory dishes almost certainly would prove resistant in a human patient, which means that such virus-resistant cancers could be identified with simple laboratory tests prior to being applied to patients, says Grdzelishvili.

"Prescreening cells against an array of different viruses could identify the best option for treating a particular tumor," says Grdzelishvili. Combined virotherapy (analogous to combination drug therapy) could also potentially lead to enhanced cancer killing. "Understanding the mechanisms and identifying biomarkers of resistance is critical for the development of prescreening approaches and individualized oncolytic virotherapy against PDA," says Grdzelishvili.

More information: A.M. Murphy, D.M. Besmer, M. Moerdyk-Schauwecker, N. Moestl, D.A. Ornelles, P. Mukherjee, and V.Z. Grdzelishvili, 2012. Vesicular stomatitis virus as an oncolytic agent against pancreatic ductal adenocarcinoma. *J. Virol.* 86:3073-3087.

Provided by American Society for Microbiology