MedicalXpress

Research identifies targeted molecular therapy for untreatable NF1 tumors

December 10 2012

Researchers conducting a preclinical study in mice successfully used targeted molecular therapy to block mostly untreatable nerve tumors that develop in people with the genetic disorder Neurofibromatosis 1 (NF1).

Scientists from Cincinnati Children's Hospital Medical Center report their findings online Dec. 10 in the Journal of Clinical Investigation.

"We can for the first time shrink the large majority of neurofibromas, at least in mice, by using a molecularly targeted treatment," said Nancy Ratner, PhD, principal investigator and program leader for the Cancer Biology and Neural Tumors Program in the Cancer and Blood Disorders Institute at Cincinnati Children's. "At present there is no treatment for these tumors and our data provide strong rationale for testing this therapy in clinical trials for NF1."

Neurofibromas are benign tumors that grow along peripheral nerves in the body. They affect up to half of the people who have NF1. In the United States alone there are 10,000 people with NF1. Fueled initially by mutation of the tumor-suppressing gene NF1, the tumors can grow to become quite large and compress vital organs. They can also transform into deadly malignant peripheral nerve sheath tumors (MPNSTs), the leading cause of death in people with NF1.

The researchers tested an existing experimental drug from Pfizer called PD0325901, which in the current study shrank NF1 tumors in over 80 percent of the mice treated. Study authors report it was "the most

dramatic result described to date for neurofibroma bearing mice."

The drug inhibits a protein called MEK, part of a molecular signaling chain that relays genetic instructions to the cell nucleus to promote cell growth. Researchers decided to test the drug after conducting a cross-species bioinformatics computer analysis of mouse and human NF1 tumors. The analysis identified genes and molecules that regulate cell signals driving the growth of neurofibromas and MPNSTs in both species.

The drug is currently being tested in human clinical trials for cancers that involve molecular components similar to those in NF1, in particular the MEK protein.

MEK is a downstream molecular target for a group of cell signaling proteins called Ras-GTPase. The proteins work together in a molecular relay to activate normal cell growth. In the instance of genetic mutation, Ras-GTPase can get stuck in the "on" position and promote hyperactive cell growth, tumor formation or cancer. Overactive Ras-GTPase signaling has been linked to a number of cancers.

In the case of mouse and human NF1 tumors, bioinformatics computer analysis suggested that deregulated Ras-GTPase signaling prompted MEK to stimulate the sustained activity of an enzyme called ERK. To confirm whether this molecular pathway is critical to NF1 tumor growth, researchers tested the MEK-blocking drug in genetically engineered mice.

The mice lacked expression of the NF1 gene and its tumor suppressing protein, causing the animals to develop benign neurofibromas. Scientists also transplanted human malignant peripheral nerve sheath tumor cells into a separate group of genetically receptive mice, which developed their own cancerous tumors.

Researchers then tested different doses of the drug to identify an optimal dose – one that would achieve the maximum amount of tumor shrinking efficiency with the least amount of toxicity. Treatment with PD0325901 reduced the abnormal growth of cells in both benign neurofibromas and malignant peripheral nerve sheath tumors (MPNSTs). It also reduced the volume of tumor feeding blood vessels.

Treated mice with benign neurofibromas had significant shrinkage of their tumors after 60 days, compared to untreated mice. In mice implanted with human MPNSTs, the drug diminished cancerous tumor growth and doubled survival time to 52 days, as compared to untreated animals.

Researchers said overall shrinkage of MPNSTs was modest compared to that achieved in benign tumors, possibly because additional molecular pathways are involved in their formation. They said this suggests that MPNSTs may require a combinatory treatment that includes PD0325901 in conjunction with other therapies.

Mutations of the NF1 gene are frequently found in other cancers, such as glioblastoma, lung adenocarcinoma and ovarian cancer. The researchers said this could open the possibility of studying the Ras-MEK-ERK pathway as molecular target for treating these diseases.

More information: Normal hematopoiesis and neurofibromin-deficient myeloproliferative disease require ERK, *Journal of Clinical Investigation*, 2012.
Sustained MEK inhibition abrogates myeloproliferative disease in Nf1 mutant mice, *Journal of Clinical Investigation*, 2012.
MEK inhibition exhibits efficacy in human and mouse neurofibromatosis tumors, *Journal of Clinical Investigation*, 2012.

Provided by Cincinnati Children's Hospital Medical Center