MedicalXpress

Targeting downstream proteins in cancer-causing pathway shows promise in cell, animal model

November 13 2012

The cancer-causing form of the gene Myc alters the metabolism of mitochondria, the cell's powerhouse, making it dependent on the amino acid glutamine for survival. In fact, 40 percent of all "hard-to-treat" cancers have a mutation in the Myc gene.

Accordingly, depriving cells of glutamine selectively induces programmed cell death in cells overexpressing mutant Myc.

Using Myc-active neuroblastoma cancer cells, a team led by Howard Hughes Medical Institute (HHMI) investigator M. Celeste Simon, Ph.D., scientific director for the Abramson Family Cancer Research Institute (AFCRI), identified the proteins PUMA, NOXA, and TRB3 as executors of the glutamine-starved cells. These three proteins represent a downstream target in the Myc pathway at which to aim drugs. Roughly 25 percent of all neuroblastoma cases are associated with Myc-active cells.

The findings appear in this week's issue of *Cancer Cell*. Simon is also a professor of Cell and Developmental Biology at the Perelman School of Medicine, University of Pennsylvania. The Penn team collaborated with colleagues from The Children's Hospital of Philadelphia (CHOP) John Maris and Michael Hogarty.

"These findings come from studies of fundamental cellular pathways and

would not have been discovered without ongoing support for basic research," notes Simon. "Translational research is very important, but equal emphasis on basic research of processes such as cellular metabolism is critical for the ultimate cure of cancer."

Glutamine depletion in Myc-mutant cells induces cell death through a complicated series of molecular switches involving the three protein executors and the DNA-binding protein ATF4. Knowing this, the team showed that either agonists of ATF4 or inhibitors of glutamine metabolism potently caused cell death in assays using neuroblastoma cells and inhibited tumor growth in transgenic mice. Drugs in these two classes have been approved by the Food and Drug Administration and are being tested in clinical trials for other disorders.

Provided by University of Pennsylvania School of Medicine