Colon cancer may yield to cellular sugar starvation

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Scientists at the Johns Hopkins Kimmel Cancer Center have discovered how two cancer-promoting genes enhance a tumor's capacity to grow and survive under conditions where normal cells die. The knowledge, they say, may offer new treatments that starve cancer cells of a key nutrient - sugar. However, the scientists caution that research does not suggest that altering dietary sugar will make any difference in the growth and development of cancer.

"Cancer cells adapt to living within the inner layers of a tumor, a place where circulating nutrients are relatively scarce," says Nickolas Papadopoulos, Ph.D., associate professor at the Johns Hopkins Kimmel Cancer Center. "We wanted to know what makes these cancer cells survive under such conditions."

Working with colorectal cancer cell lines that carry two of the most common cancer genes - KRAS and BRAF - they went on a hunt for genes that were controlled by KRAS and BRAF and allowed cancer cells to be more fit for survival. Nearly half of all colon cancer patients carry KRAS mutations in their tumors and another five percent of these patients have alterations in BRAF. The findings are published online in the August 6 issue of Science Express.

Their hunt quickly narrowed to one gene, GLUT1, which was consistently turned on at high levels in cells laden with KRAS and BRAF mutations. Proteins made by GLUT1 are located on the cell surface and transport glucose into cells' interiors. With increased expression of the

GLUT1 gene, cells make more GLUT1 transporters and ingest more glucose.

"We think increased GLUT1 is a survival adaptation that makes cancer cells very efficient at gathering what little sugar exists in these areas," says Bert Vogelstein, M.D., director of the Ludwig Center for Cancer Genetics and Therapeutics and Clayton Professor of Oncology at the Johns Hopkins Kimmel Cancer Center, as well as Investigator in the Howard Hughes Medical Institute. In various experiments, the Johns Hopkins investigators tested how cancer cells with KRAS and BRAF mutations fare in both standard and low glucose conditions, comparing them with so-called "wildtype" cancer cells that do not have the KRAS or BRAF gene mutations.

In one set of experiments, they placed both types of cancer cell lines - those with KRAF/BRAF mutations or without -- in lab dishes with normal and high glucose environments. In the glucose-depleted environment, cells with KRAS/BRAF mutations had far better uptake of glucose than wildtype cells. When they knocked out the GLUT1 gene, this difference disappeared.

Next, the scientists tested whether cancer cells with KRAS/BRAF mutations would outpace growth of cells without these mutations. They mixed both groups of cells together and placed them in normal and low glucose environments. Both sets grew equally well in normal conditions, but on the lab dishes with low glucose, cancer cells with the KRAS/BRAF mutations survived while those without the mutations quickly died. As a result, the KRAS/BRAF mutant cells rapidly became the predominant cell in the population. "These gene mutations clearly give colon cancer cells the ability to grow in sugar-depleted environments, such as those in tumors," says Papadopoulos.

To determine whether this metabolic change could be used to treat

tumors with KRAS or BRAF mutations, the team tested an investigational drug called bromopyruvate, which inhibits glucose metabolism. Results showed that the drug blocked cancer growth in mice with implanted human tumors containing KRAS or BRAF mutations and had no toxic side effects in the mice.

Source: Johns Hopkins Medical Institutions

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