

Cancer cells 'reprogram' energy needs to grow and spread, study suggests

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Studying a rare inherited syndrome, researchers at Johns Hopkins have found that cancer cells can reprogram themselves to turn down their own energy-making machinery and use less oxygen, and that these changes might help cancer cells survive and spread.

The Hopkins scientists report that the loss of a single gene in kidney cancer cells causes them to stop making mitochondria, the tiny powerhouses of the cell that consume oxygen to generate energy.

Instead, the cancer cells use the less efficient process of fermentation, which generates less energy but does not require oxygen. As a result, the cancer cells must take in large amounts of glucose. The appetite of cancer cells for glucose is so great that it can be used to identify small groups of tumor cells that have spread throughout the body.

Although changes in mitochondria have been described in many cancers, the Hopkins study shows for the first time how a cancer-causing mutation can block their production.

"There must be a strong advantage to cancer cells to stop using a highly efficient process in favor of one that generates much less energy," says Gregg Semenza, M.D., Ph.D., professor of pediatrics and director of the vascular biology program in the Institute for Cell Engineering at Johns Hopkins.

But turning down the "thermostat" in a sense, may give the cancer cell a

survival edge. Reporting in the May 8 issue of *Cancer Cell*, Semenza and his colleagues found that if they reversed the switch and forced kidney cancer cells to start making mitochondria again, the cells produced increased amounts of free radicals, which can cause cells to stop dividing or even die.

Semenza's team uncovered the mitochondrial mechanism in a study of Von Hippel-Lindau (VHL) syndrome, caused by a single gene mutation and characterized by the tendency to develop tumors in many parts of the body, including the kidney, brain and adrenal glands.

Semenza and colleagues measured mitochondria content and oxygen use in kidney cancer cells that contain no VHL protein and in the same cells with VHL "engineered" back in. Restoring VHL caused the cells to make two to three times more mitochondria and use two to three times more oxygen.

VHL normally blocks the action of HIF-1, a protein that the Hopkins group discovered in 1992. Cells normally make HIF-1 only under low oxygen conditions, when fermentation is necessary to make energy. However, in the absence of VHL, HIF-1 is active even when oxygen is plentiful and switches on genes that help a cell take up more glucose.

This current work shows that excess HIF-1 counteracts a protein called MYC, which normally stimulates cells to make mitochondria. "Because MYC is turned on in many other cancers, these results suggest that shutting down the mitochondria must be a very important event in kidney cancer," Semenza notes.

There is currently no treatment available for patients with advanced kidney cancer. Scientists at pharmaceutical companies, the National Cancer Institute, and laboratories at Hopkins and other universities are investigating whether drugs that inhibit HIF-1 may be useful for cancer

therapy.

Source: Johns Hopkins Medical Institutions

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