Scientists find cancer cells co-opt fat metabolism pathway to become more malignant

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An enzyme that normally helps break down stored fats goes into overdrive in some cancer cells, making them more malignant, according to new findings by a team at The Scripps Research Institute.

"Historically, research has focused on the mechanisms leading to cancer formation and therapies have focused on taking out cancer cells," says Benjamin Cravatt, chair of the Scripps Research Department of Chemical Physiology and corresponding author of the study published in the January 8, 2009 issue of the journal *Cell*. "But here we were looking for pathways that lead to cancer aggressiveness."

The aggressiveness-promoting enzyme, called monoacylglycerol lipase (or MAGL for short), may provide a new target for treating more malignant forms cancers or for preventing cancer progression. The findings also suggest an explanation for the reported link between obesity and cancer by showing that releasing stored fats in cancer cells can push them toward more aggressive behaviors.

Homing in on a Cancer Protein

As a cancer grows inside the body, some cells take on more aggressive characteristics, such as the ability to invade local areas and to spread to other parts of the body. To identify possible drivers in this process, Daniel Nomura, a postdoc in Cravatt's lab, compared changes in the

functional state of enzymes in non-aggressive cancer cells to that of aggressive ones.

"We were looking for changes in enzyme activity," explains Nomura. In particular, the researchers were focusing on a group of enzymes, called serine hydrolases, that break down proteins, fats, and other molecules in cells. "This is one of the largest known enzyme families, comprising about one percent of all proteins in a cell," says Nomura. "And these enzymes have been implicated in cancer and other diseases."

Nomura employed a technique pioneered in Cravatt's lab called activity-based protein profiling, which allows researchers to survey all active enzymes in a cell at once. By using a fluorescent label that only "tags" enzymes with certain chemical properties, they were able to selectively sort through all the enzymes belonging to the serine hydrolases family, looking for ones that are abnormal in aggressive cancers.

Among the many enzymes detected, MAGL—a type of enzyme, called a lipase, that breaks down stored fats, or lipids—stood out as being highly elevated in aggressive cancers. Through a series of experiments where Nomura either inhibited or stimulated MAGL's activity, they were able to establish that this enzyme is capable of converting cancer cells from less to more malignant forms.

"It is not only necessary but sufficient for the aggressive phenotype," says Cravatt, who is also a member of the Skaggs Institute for Chemical Biology at Scripps Research.

Identifying a New Metabolic Pathway

Having identified a key player responsible for the aggressive behavior of cancer cells, Cravatt and Nomura wanted to better understand MAGL's role.

They discovered that when the MAGL becomes more active in cancer cells it breaks down stored fats to produce large amounts of free fatty acids—the building blocks of cell membranes and of fatty molecules that serve as signals to and from cells. These free fatty acids then go on to produce other smaller molecules known to promote cancer growth and progression.

MAGL was known to break down stored fats, but had never been shown to regulate free fatty acid production. "So this told us that it is an acquired activity of aggressive cancer cells," says Nomura. "As cancer cells become more aggressive, the lipase is increased and its activity is targeted to the release of free fatty acid." In other words, cancer cells co-opted MAGL's activity to support their progression.

Explaining the Link to Obesity

The finding that MAGL regulates the production of free fatty acids in aggressive cancer cells provides a possible explanation for the reported link between obesity and cancer.

People who eat foods high in fats are constantly introducing free fatty acids in their bodies. "We have shown that cancer cells have their own pathways to produce free fatty acids, which will enable them to become more aggressive," says Cravatt. "Less malignant cancer cells do not appear to have yet adopted an autonomous pathway to increase their own pools of free fatty acids. Thus, taking free fatty acids from the diet could assist these cells in developing a more malignant phenotype."

Many more experiments are needed to evaluate whether blocking MAGL's activity might serve to curb cancer's progression in people, which could offer a new type of cancer therapy. Because the enzyme is not needed for cell survival—rather for progression to more aggressive behaviors—it may offer some advantages over existing therapies.

"It might have a better safety profile because it does not target a general survival mechanism common to all cells," explains Cravatt.

In addition to Cravatt and Nomura, co-authors of the study "Monoacylglycerol Lipase Regulates a Fatty Acid Network that Promotes Cancer Pathogenesis" also include Jonathan Long, Sherry Niessen, and Heather Hoover from Scripps Research and Shu-Wing Ng from Harvard Medical School.

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