Molecular Switch Links High-Fat Diet to Prostate Cancer Metastasis

The findings raise the possibility that changes in diet could potentially improve treatment outcomes in some men.

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A new study in mice has revealed a molecular link between a high-fat diet and the growth and spread of prostate cancer. The findings raise the possibility that changes in diet could potentially improve treatment outcomes in some men, the study leaders believe.

In the study, the researchers also showed that an anti-obesity drug that targets a protein that controls fat synthesis could potentially be used to treat metastatic prostate cancer.

The study, funded by NCI, was published in Nature Genetics on January 15.

Population studies have long suggested that diet influences prostate cancer risk, including the risk for developing metastatic cancer. For example, until recently, the disease was relatively rare in Asia, where diets have been typically lower in fat than in the West. Studies have shown, however, that when men emigrate from Asia to the United States and adopt western dietary habits, their risk for prostate cancer rises to that of other Americans.

This new study is important because it details specific molecular changes induced by a high-fat diet in cells and animals and shows the impact on prostate cancer metastasis, said Yusuf Hannun, MD, director of the Stony Brook University Cancer Center in New York, who studies lipids and their role in cancer but was not involved in the study.

Insights from a Mouse Model

The study’s lead author, Pier Paolo Pandolfi, MD, PhD, of Beth Israel Deaconess Medical Center, has studied a tumor suppressor gene called PML for almost 30 years, since he helped discover it and its association with leukemia. The new study began when his research group observed that PML is deleted (or lost) in 20 percent of human metastatic prostate cancer and decided to test whether turning the gene off in mice promotes prostate cancer.

Another tumor suppressor gene called PTEN has long been known to be important in prostate
cancer; the gene is at least partially lost in 70 percent of human prostate cancer, and complete loss of the gene is common in metastatic prostate cancer.

The researchers at Beth Israel had a line of mice bred to lack the PTEN gene. These mice did tend to eventually develop prostate tumors, but the tumors were not invasive. The research group decided to see if knocking out PML in the mice that already lacked PTEN would speed up prostate cancer growth.

“The first surprise was that PML loss not only accelerates the development of prostate cancer, but it accelerates the metastatic spread of prostate cancer,” Pandolfi said. Metastatic prostate cancer had rarely been seen in mice before, he explained.

When the researchers compared the non-metastatic tumors in the PTEN-lacking mice with the metastatic tumors in mice that also lacked PML, they found that the metastatic tumors were full of fat. They repeated the experiment in cultured human cells. Looking deeper into the mice and human cells’ biochemical pathways, the researchers found that the loss of PML had activated a protein called SREBP, a central regulator of fat pathways in the body, and made the cells churn out fat molecules.

If losing PML leads prostate cancer cells to make fat and metastasize, could fat from the diet also promote prostate cancer, Pandolfi’s team wondered.

“Epidemiologically, there is extremely compelling data that if you are obese or eat a certain diet, for example a fast-food diet, you are at risk of developing cancer and of developing aggressive cancer,” Pandolfi said. It suddenly occurred to him that the reason metastatic prostate cancer was rarely seen in mouse models might be because lab mice tend to eat a vegetable-rich chow that is low in fat and sugar.

The research group decided to swap out the vegetable-rich chow for lard-laden pellets. “The shocking, eye-opening outcome of this was that all the mouse models, even those that hadn’t lost PML and never metastasized on chow, started developing aggressive and metastatic prostate cancer,” Pandolfi said.

Targeting Fat Pathways

Lipids have a complex and important role in maintaining normal cell structure and function. “However, too much lipid is not good for the cell,” said Rihab Yassin, PhD, a program director in NCI’s Division of Cancer Biology. “This study outlines an important mechanism by which high fat promotes aggressive and metastatic prostate cancer. It also underscores the role of the tumor suppressor gene PML in regulating cellular [fat production] and how PML loss could drive an aggressive disease.”

In animal models, high-fat diets have been found to increase the risk for several cancers, including prostate, mammary, and colon cancers, said Hannun. But, he added, the new study provides a
mechanism by showing that, like the loss of PML, a high-fat diet can trigger the uncontrolled activity of SREBP.

“The good news for patients is that a number of pharmaceutical companies have developed drugs that target SREBP to treat obesity,” said Pandolfi. His group treated mice bearing prostate tumors with one such drug, called fatostatin. They found that fatostatin (which has not been approved by the Food and Drug Administration for any use) blocked both prostate tumor growth and metastasis in mice with SREBP overactivity caused by PML loss.

Soon after the findings from this study were published, Pandolfi was contacted by companies that produce other SREBP inhibitors intended to treat obesity and are interested in investigating whether the drugs could be repurposed for a role in cancer treatment.

The Complexities of Diet

The study shows that the body’s internal fat production processes are an important part of the life history of cancer cells, but the study doesn’t definitively show that a high-fat diet rather than obesity is what promoted cancer, Hannun said. Jill Hamilton-Reeves, PhD, a nutritionist who studies prostate cancer at the University of Kansas Medical Center, agreed.

In addition, “it is important to note that the two different diets fed to the mice differed in more ways than just the percent fat content,” she said, adding that the mice on a high-fat diet consumed 60 percent of their calories from fat, well above the 20 percent to 40 percent of calories from fat in the average Western diet.

She pointed out that, in addition to lard, the high-fat pellets contained sugar, starch, and many other ingredients not found in the regular chow, which contained healthier ingredients such as whole wheat, fish meal, and wheat germ. The mice on the high-fat diet quickly gained weight, while the mice on the control diet maintained their weight.

“Overall diet patterns generally are more relevant to health than any single isolated nutrient,” Hamilton-Reeves said.

“We need to understand which fat is good, which fat is not,” said Pandolfi. He can envision a future of precision medicine for patients with cancer that includes specific recommendations for diet. Based on a cancer’s genetic mutations and metabolic profile, a patient might be advised to eat or avoid certain foods, take a particular medicine, or proceed with surgery.

“The core of the story is that we have a mechanism,” Pandolfi said. “You can see the interplay between the environment and genes.” At that interface, helpful interventions seem within reach, he added.

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