Cell pathway on overdrive prevents cancer response to dietary restriction

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Whitehead Institute researchers have pinpointed a cellular pathway that determines whether cancerous tumors respond to dietary restriction during their development.

Studying human cancer cell lines in mice, researchers have found that when this pathway, known as PI3K, is activated permanently via mutation, tumors grow and proliferate independent of food consumption. However, when the PI3K pathway operates normally, dietary restriction (defined as a 60% reduction in normal intake), results in smaller tumors. The findings are published online in the March 11 issue of *Nature*.

"Our findings indicate that each tumor cell bears a signature that determines whether or not that cell will be affected by dietary restriction," says Nada Kalaany, first author of the paper and a postdoctoral researcher in the lab of Whitehead Member David Sabatini. "We think that mutations in the PI3K pathway are a major determinant of the sensitivity of tumors to dietary restriction."

The connection between food consumption and tumor growth is not new. In the early 20th Century, scientists first noted the correlation between a restricted diet and decreased tumor size and incidence. However, some cancers' growth rate was unaffected by a decrease in food consumption. The reason for this difference remained unclear.

To determine how various tumor types are affected by dietary resistance, Kalaany injected cells from human prostate, breast, brain, and colon

cancers into mice in an experimental protocol used frequently to study human cancers. The mice then ate as much as they liked (control group) or received 60% of the caloric intake of their counterparts (the dietary restriction (DR) group). Both groups ingested the same amounts of vitamins and minerals. After a few weeks, Kalaany saw that the cancers could be divided into DR-sensitive tumors, with significantly lower tumor volumes in the DR mice than in control mice, or DR-resistant tumors, whose sizes were apparently unaffected by normal or restricted diets.

Kalaany then grew the same cancer cells in Petri dishes to see how the DR-sensitive and DR-resistant cancers respond to food-related hormones in the body. The cancers were grown solutions containing increasing amounts of insulin, insulin-like growth factor 1 (IGF1) or in a solution without these hormones. The results supported the previous experiment: those cancer cells that were DR-sensitive in the mice were also stunted by a lack of insulin and IGF1; those cancer cells that were DR-resistant in the mice were unaffected by changes in insulin and IGF1 levels.

Because the difference between the two groups was sensitivity or insensitivity to insulin and IGF1, Kalaany thought the insensitive tumors may have something amiss in a cellular process called the PI3K pathway, which is activated by insulin/IGF1. A search for mutations in two genes found in the PI3K pathway that are often associated with cancer (PI3KCA and PTEN), revealed that DR-resistant cells had mutations in one or the other of the genes, while DR-sensitive cells showed no such mutations.

Using a DR-resistant tumor cell line in which the PTEN gene could be switched on or off, Kalaany tested whether a change in the PTEN gene alone could affect a tumor's sensitivity to DR. When the PTEN gene was turned off, the cancer cells were not affected by dietary restriction, and tumor size increased similarly in control and DR mice. But when PTEN

was turned on, thereby restoring normal function to the PI3K pathway, the cells became sensitized to dietary restriction and tumor size was smaller in the DR group.

This research was confirmed in two mouse models of cancer, one with prostate cancer caused by PTEN deletion and one with lung cancer and a functioning PTEN gene. Again, the mice without the PTEN gene did not respond to dietary restriction, but the mice with a functioning PTEN gene were sensitive to dietary restriction.

Sabatini says that Kalaany's results could lead to cancer treatments tailored to the characteristics of an individual patient's tumor cells.

"Her findings suggest that if we have therapies that mimic dietary restriction, we could better predict which tumors would respond to those dietary restriction-mimicking drugs and which ones would not," says Sabatini.

Sabatini is also intrigued by the inverse relationship between too much food and an increase in tumors. "We already know that the United States has an epidemic of obesity and that obesity is probably the biggest contributor to cancer in the U.S., even more so than smoking. Does this research have anything to do with that correlation between obesity and cancer, that if we make animals really obese, that this pathway is also involved in determining their sensitivity to cancer? Answering that question is the next step."

More information: "Tumours with PI3K activation are resistant to dietary restriction" *Nature*, online March 11, 2009, Nada Y. Kalaany & David M. Sabatini

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