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Dietary glucose affects the levels of a powerful oncogene in mice

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An animal study conducted by researchers at Georgetown Lombardi Comprehensive Cancer Center raises questions about the consequences of diet—specifically glucose, the plant-based sugar that fuels cell life—on increased activity of an oncogene that drives tumor growth.

In the study published online today in the journal *Cell Cycle*, the scientists report, for the first time, that high levels of glucose in the diet of mice with cancer is linked to increased expression of mutant p53 genes. Normal p53 acts as a tumor suppressor, but many scientists believe that mutant p53 acts as an oncogene, pushing cancer growth. High levels of mutant p53 expression in a wide variety of human tumors has long been linked to cancer aggressiveness, resistance to therapy, worse outcomes and even relapse after therapy.

The findings do not mean that cancer patients should cut back on the sugar in their diets, says the study's senior investigator, Maria Laura Avantaggiati, M.D., associate professor of oncology at Georgetown Lombardi Comprehensive Cancer Center, part of Georgetown University Medical Center (GUMC).

"We have not studied the effect of glucose on cancer growth in humans, so we cannot make that link at this point," she says. "Furthermore, there are many different types of p53 mutations and we have studied only some of them. But if we can show that this is a generalized phenomenon, it could have important implications for care, and may help explain the observation that human diet does affect cancer treatment and growth."

Avantaggiati adds that the study tested different components of the diet and found that complete starvation, among other factors, did not have any effect on the levels of mutant p53 in laboratory-cultured cancer cells. She also adds that specific research examining if different components of the diet, aside from glucose, will contribute to the growth of tumors harboring p53 mutations is necessary.

In the study, the researchers sought to understand how to reduce the levels of proteins generated by mutations of the p53 gene in tumors. The issue is important, Avantaggiati says, not only because the majority of human tumors contains too much mutant p53 protein, but also because researchers now believe that current chemotherapy drugs actually increase the amount of mutant p53 in cancer, leading to possible resistance to these drugs.

In the five-year study, conducted in collaboration with her GUMC colleagues and co-authors Chris Albanese, Ph.D., and Olga Rodriguez, M.D., Ph.D., the researchers studied the link between glucose restriction and autophagy in cultured cells. Autophagy is a process that clears a cell of damaged organelles and misfolded proteins—proteins viewed to be dysfunctional.

"Mutant p53 proteins are misfolded, but they are usually not efficiently degraded. However, when autophagy is induced by glucose restriction, this process eliminates them, and this is what we were hoping to see," Avantaggiati says. But the process offers an additional bonus. Autophagy is usually turned-off by mutant p53, but because these cancer cells now contain very little p53 protein, autophagy marches on, chewing up proteins, pushing the cancer cell to die.

The researchers then conducted a series of studies to see if this link could be established in animal models. In a transgenic mouse model with mutant p53, they showed that in mice fed a low carbohydrate (low

glucose) diet—but one with a normal calorie load—there was a significant decrease in the amount of mutant p53 protein in their tissues, compared to mice fed with a high carbohydrate diet.

This suggested that mutant p53 levels are sensitive to glucose restriction, but additional research was needed to determine whether this phenomenon had an impact upon tumor growth.

To help answer that question, other experiments were conducted to test the ability of human lung cancer cells, engrafted in mice, to grow when the animals were fed one of two diets—low or high carbohydrates. In this case the researchers constructed a p53 mutant protein that was less susceptible to degradation by glucose restriction-induced autophagy.

They found that in the mice fed the low carbohydrate diet, the growth of tumors was blocked, but only when the tumors expressed the mutant p53 protein that could be degraded by autophagy. But when the artificial mutant p53 proteins could not be cleared, cancer growth proceeded regardless of the glucose content in the diet. This suggested that p53 mutant degradation is part of the reason why the low carbohydrate diet slows tumor growth, Avantaggiati says.

"This series of studies helps establish the mechanisms of why a low carbohydrate diet slows tumor growth," says Avantaggiati. "Glucose restriction triggers autophagy, a critical process for clearing the cell of detrimental, potentially damaging proteins or cellular debris that can eventually destroy the entire cancer cell. We believe that this process works more efficiently when mutant p53 is not around."

The findings are very compelling, she says, and should set the ground for investigating, in further depth, how glucose and various food components affect the levels of mutant p53 in tumors. "Various types of dietetic interventions have been shown to affect cancer growth, but no

one had ever shown, before this study, that the amount of carbohydrates could affect the expression of mutant p53," Avantaggiati says. "However, we need to be cautious about translating a finding from mice to humans. Our research into that connection is ongoing."

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