Altering Diet Enhances Response to Cancer Treatments in Mice

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People must eat to survive. And the cells that make up the body eat too. Or more accurately, cells break down and rebuild food into the individual molecules they need to stay alive and grow. This complex network of processes is called cellular metabolism.

Cancer cells can alter their metabolism to survive, so targeting cancer cell metabolism has become of great interest to researchers. Questions being asked include: Is it possible to attack a tumor's nutritional needs as part of cancer treatment? And could this be done by tweaking a cancer patient's diet?

A new NCI-supported study suggests that the latter may be possible. In the study, researchers showed that feeding mice a diet very low in the nutrient methionine improved the ability of chemotherapy and radiation therapy to shrink tumors.

When the researchers tested a low methionine diet in six healthy adults, methionine levels in their bodies fell and they experienced metabolic changes similar to those seen in the mouse studies. However, the study was not designed to test the effect of methionine restriction on cancer treatment in humans.

The concept of using specific dietary changes to enhance cancer treatment "is really at the very early stages," said Jason Locasale, PhD, of Duke University, who led the new study. "And there's not going to be one be-all, end-all diet for [treating] cancer. But these aspects of diet seem to have all kinds of really interesting effects on cancer outcomes, and we have to take them seriously."

A Dietary Vulnerability

Methionine is an essential amino acid that plays an important role in cellular metabolism. The body cannot produce methionine from scratch, so it must come from food. Methionine is most prevalent in animal products, such as lean meat and eggs, but also can be found in lower quantities in plant sources.

Normal cells can also recycle methionine that has already been taken into the body, explained Michael Espey, PhD, of NCI's Division of Cancer Biology, who was not involved in the study. But some cancer cells lose this ability when they mutate, he added. This means that they become completely reliant on the diet for their methionine requirements.

Methionine is needed by cells to repair damaged DNA and reduce oxidative stress, Espey explained. So depleting methionine from cancer cells targeted by DNA-damaging therapies, such as chemotherapy or radiation therapy, "may enhance the ability of these treatments to kill the cancer cells," he said.

"Cancer researchers recognized this feature and surmised that methionine could be a potential weakness, because anything that a cancer cell has become reliant on is a good target, as long as you have some sort of treatment to attack that vulnerability," said Espey.

In their study, Locasale and his colleagues first measured whether cutting the amount of methionine in the diet of mice could quickly reduce the amount of methionine available to cells in the body. They found that switching mice to a diet about seven times lower in methionine than normal reduced the levels in cells after 2 days.

They then fed the low methionine diet to mice carrying tumors derived from either of two types of human cancer cells. Methionine restriction alone greatly slowed the growth of tumors derived from one of the cell lines, and slowed it somewhat in tumors derived from the other cell line.

Enhancing Treatment Effects

The researchers next tested whether adding dietary methionine restriction to cancer treatments in mice could magnify the effects of those treatments.

In mice bearing tumors derived from human colorectal cancer, low doses of the DNA-damaging chemotherapy drug 5-fluorouracil (5-FU) failed to shrink the tumors. But when the mice were fed the methionine-restricted diet during 5-FU treatment, their tumors shrank. Analyses of metabolism showed that the production of molecules needed to repair DNA, which requires methionine, had been altered as expected.

The researchers also tested the combination of methionine restriction and radiation therapy in mice engineered to grow aggressive soft tissue sarcomas. The combination of the methionine-restricted diet plus radiation therapy slowed tumor growth by about 50% compared with the combination of a normal diet plus radiation.

More Knowledge Needed

In a proof-of-concept follow-up experiment, six healthy middle-aged adults were recruited to eat a low methionine diet for 3 weeks. The diet contained about 80% less methionine than an average normal diet. Protein was mainly supplied through a methionine-free dietary supplement. The diet also included fruits, vegetables, and refined grains, which are naturally low in methionine.

In the human study, the low methionine diet quickly reduced the amount of the amino acid available to participants' cells and altered the cells' metabolism, similar to what the researchers had observed in mice fed a methionine-restricted diet.

Methionine restriction "is a potential strategy" to treat cancer, Espey said. "But more research is needed into the correct dose and timing, and the amount of restriction that's necessary to balance the positive effects on enhancing cancer therapy versus the negative effects on the body's normal physiology."

Among other things, methionine is needed to maintain nerve cells and muscle mass, he added. "So there could potentially be side effects of restricting methionine in the diet [in the long term]."

"We can speculate that there's going to be all kinds of interesting nutritional interventions that could influence cancer, but we're nowhere near the point of really being able to prescribe these dietary interventions," added Locasale.

For other diseases where metabolism is known to play an important role—such as cardiovascular disease and diabetes—dietary interventions are an important part of treatment, Locasale said.

"Over the last 10-15 years, we've come to understand that cancer also has a huge metabolic component to it," he continued. "Cancer cells have different nutrient requirements and different metabolic demands than normal tissue. But we have almost no knowledge of how nutrition might influence demands. We're just starting [to learn] right now."

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