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Leucine deprivation proves deadly to malignant melanoma cells

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Whitehead Institute researchers have found that depriving human melanoma cells of the essential amino acid leucine can be lethal to the cells, suggesting a possible strategy for therapeutic intervention.

The researchers observed the effect in melanoma cells with a mutation in the RAS/MEK signaling pathway—the most common mutation found in the deadliest form of skin cancer.

Leucine is one of nine essential amino acids humans must ingest, as we are unable to synthesize them. These nine, along with 12 non-essential amino acids, are the building blocks of proteins used in muscle production and normal cell functions. Cellular amino acid levels and other nutrients are monitored by the mTOR pathway. Typically, when levels of one or more amino acids drop too low, the mTOR pathway is turned off, which activates a process called autophagy.

During autophagy, the cell attempts to boost amino acid levels by breaking down the cell's protein-based structures back into their amino acid components. This is similar to the entire body breaking down fat and muscle when it is on a diet. For a cell, autophagy is a short-term survival mechanism.

According to their paper published in the May 17 issue of *Cancer Cell,* researchers in the lab of Whitehead Institute Member David Sabatini found that melanoma cells with RAS/MEK pathway mutations short-circuit this chain of events.

"The odd thing is that if you remove this one essential amino acid, leucine, the melanoma cells don't activate autophagy," says Sabatini, who is also a professor of biology at MIT and a Howard Hughes Medical Institute (HHMI) investigator. "Because leucine is essential, they eventually die. Potentially, that could be used as a way of targeting the melanoma cells if one could mimic the lack of leucine."

When melanoma cells with RAS/MEK pathway mutations are deprived of leucine, mTOR does not sense it, so mTOR does not turn off, and autophagy never begins. Instead, the cells behave as if there were no nutrient shortage until they reach a metabolic crisis and die.

Although cells in a test tube can be deprived of leucine completely, removing leucine from a mouse or a human is almost impossible, due to large leucine reservoirs in muscles. To test how leucine deprivation works in an animal model, Joon-Ho Sheen, who is first author of the Cancer Cell paper, implanted human melanoma tumors with RAS/MEK pathway mutations into mice. He then fed the mice a leucine-free diet. Within a few days, the leucine concentration in the mice's blood dropped from about 110 micromoles to 60 or 70 micromoles. As the blood leucine levels dropped, so too did the leucine levels within the mice's cells. Still, the drop in leucine wasn't sufficient to kill the melanoma cells in vivo.

Sheen then gave the mice the drug chloroquine along with a leucine-free diet. Chloroquine, which is an anti-malaria drug, inhibits autophagy. With the one-two punch of chloroquine and a leucine-free diet, the melanoma cells died, significantly reducing tumor sizes compared with mice fed either a normal diet or a leucine-free diet without chloroquine.

For Sheen, these results raised more questions, particularly with regard to potential therapeutic applications.

"Thanks to the pioneering work by others in the autophagy field, we were able to show that leucine deprivation triggers apoptosis in melanoma cells. I think our work provides a framework, but there are many areas to fill in," says Sheen, who is a postdoctoral researcher in the Sabatini lab. "In practice, how can you deprive just leucine in humans? Maybe using some sort of enzyme that degrades leucine or a small molecule inhibitor that blocks leucine's uptake by cells. And we need a better way to target autophagy; chloroquine isn't very efficient at this. And those are just the immediate, foreseeable issues."

More information: "Defective regulation of autophagy upon leucine deprivation reveals a targetable liability of human melanoma cells in vitro and in vivo" *Cancer Cell,* May 16, 2011.

Provided by Whitehead Institute for Biomedical Research