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Molecule effectively starves cancer cells

Overcoming an addiction is most often the healthy choice. But for cancer cells, their addiction to glutamine is life-giving. Turbo-charged engines capable of metastasizing in even the most difficult of conditions, cancer cells find their strength in glutamine, an amino acid important to protein metabolism and a key nutrient for the growth of cancer cells. Researchers have long believed that starvation – breaking the glutamine addiction – may be an effective strategy in the fight against some cancers, but for decades have struggled with how to accomplish this feat.

Scientists at Cornell's College of Veterinary Medicine in the Department of Molecular Medicine and at the Department of Chemistry and Chemical Biology in the Arts College have discovered a molecule that inhibits cancer growth by blocking its utilization of glutamine. The finding could lead to a new class of drugs, capable of stopping the progression of cancer without harming normal cell growth. The molecule, dubbed 968 by investigators, binds to glutaminase, an enzyme used to support the glutamine addiction. The ability of 968 to block the actions of this enzyme makes it a key player in the effort to deprive cancer cells from the elements necessary to support their hyperactive metabolic profile.

"Cancer cells demand a tremendous amount of energy," said Dr. Richard Cerione, the Goldwin Smith Professor of Pharmacology and Chemical Biology and senior author of "Targeting mitochondrial glutaminase activity inhibits oncogenic transformation," an article which was published this month in Cancer Cell. "One of the key enzymes that fuels the process is glutaminase, whose activation in cancer cells can be blocked by the small molecule 968."

Funded by the National Institutes of Health and the Susan G. Komen Foundation, these studies involved a decade-long research effort involving several members of the Cerione laboratory including postdoctoral associate Jianbin Wang and Senior Research Associate Jon Erickson, the co-first authors of the article. It required using a wide range of biochemical, biophysical and molecular biology-based approaches to come full circle, according to Cerione and senior research associate Kristin Wilson.

"This is the rebirth of a century-old empirical observation—that cancer cells have altered metabolisms—and further development of the discovery in the 1970s and '80s that growth factor receptors and other signaling proteins are also altered in cancer cells," said Cerione. "This new information now offers exciting possibilities for designing strategies to stop tumor growth, to effectively reverse cellular transformation."

After discovering that 968 inhibited glutaminase and effectively shrunk tumor cells in mice, Cerione and his research team tested the molecule to understand its effects on non-cancerous cells. Because the energy needs of normal cells are different than those of cancer cells, normal cellular functions are much less reliant on elevated glutamine metabolism, which means that 968 only impacts cancerous cells, according to Cerione.

"We have effectively stopped the growth of breast cancer cells in the lab without affecting normal mammary cells," said Cerione, who is currently investigating the impact of 968 on other forms of cancer, including prostrate, ovarian, and pancreatic cell lines. "We've validated our target. The next step will be to commercialize a small class of molecules capable of stopping cancer cell growth in humans."

Cerione and colleagues are currently working with the KensaGroup, of Ithaca, N.Y., to do just that, although he is quick to add that his work is not done. He will continue to explore the effects of 968 and glutaminase on cancer cells to obtain detailed information regarding how cancer cells re-program their metabolism to sustain their malignant characteristics.

"Our research has highlighted a previously unrecognized connection between the cell's metabolic machinery and the signaling pathways and growth factor receptors that regulate cell growth," said Cerione. "However, I believe that it is reasonable to suspect there is a broader role for these connections between metabolism and cell signaling, that may well impact other areas in biology and biomedicine."