Study: Molecule can starve cancer cells

Cornell University

While overcoming an addiction is usually the healthy choice, cancer cells' addiction to the amino acid glutamine is key to their vitality and growth. But Cornell researchers have discovered a molecule that can block cancer cells from using glutamine, thereby inhibiting their growth.

Researchers have long believed that starving cancer cells, little turbo-charged engines capable of metastasizing in even the most difficult of conditions, would break the glutamine addiction and help fight some cancers. But they have struggled for decades with how to accomplish this feat.

Now, they have discovered a molecule that does the job. Dubbed 968 by investigators, the molecule binds to the enzyme glutaminase, which inhibits cancer growth by blocking the cancer cells' utilization of glutamine.

"Cancer cells demand a tremendous amount of energy," said Richard Cerione, the Goldwin Smith Professor of Pharmacology and Chemical Biology in the Colleges of Veterinary Medicine and Arts and Sciences at Cornell and senior author of the research, which is the cover story in the Sept. 14 issue (Vol. 18:3) of 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."

The finding could lead to a new class of drugs, capable of halting cancer progression without harming normal cell growth, he said.

"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."

Cerione

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, Cerione said.

"We have effectively stopped the growth of breast cancer cells in the lab without affecting normal mammary cells," said Cerione, who is now investigating the impact of 968 on other forms of cancer, including prostate, 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 on 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."

Cornell co-authors of the research include postdoctoral associate Jianbin Wang (co-first author), and senior research associates Jon Erickson (co-first author), Kristin Wilson and Sekar Ramachandran.

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The glutamine addict

The cover article sketch (by Efraim Racker, the late Albert Einstein Professor of Biochemistry at Cornell and in whose honor the annual Racker Lecture is presented at Cornell every November, at which several Nobel laureates have lectured over the years, starting with James Watson of Watson and Crick double helix fame) depicts a glutamine addict (symbolizing a cancer cell). Cancer cells can become heavily reliant on glutamine metabolism to satisfy the biosynthetic and energy requirements for sustaining their malignant state. Thus, they are often referred to as being "glutamine addicted." Cornell researchers report here that they have discovered a compound that can "block the addiction" and thus intervene against cancer.

"What makes the cover especially neat is that Racker was a champion of the idea

that cancer is about altered metabolism. He was one of my mentors, and we argued about this all of the time over our weekly Saturday lunches, after I first came to Cornell as a young assistant professor," says Professor Richard Cerione. "Thus, it has all come full circle as our work has led us to the importance of glutamine metabolism in cancer and so we thought it would be neat in a way to honor Ef's ideas with a cover that used one of his sketches (in addition to being an outstanding scientist, he was a prolific artist and his paintings hang in some of the leading research institutions throughout the world)."

Stephanie Specchio is director of communications at the College of Veterinary Medicine

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