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A new way to fight cancer: the silver shield

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Fasting for two days protects healthy cells against chemotherapy, according to a study appearing online the week of Mar. 31 in *PNAS Early Edition*. Mice given a high dose of chemotherapy after fasting continued to thrive. The same dose killed half the normally fed mice and caused lasting weight and energy loss in the survivors.

The chemotherapy worked as intended on cancer, extending the lifespan of mice injected with aggressive human tumors, reported a group led by Valter Longo of the University of Southern California.

Test tube experiments with human cells confirmed the differential resistance of normal and cancer cells to chemotherapy after a short period of starvation.

Making chemotherapy more selective has been a top cancer research goal for decades. Oncologists could control cancers much better, and even cure some, if chemotherapy were not so toxic to the rest of the body.

Experts described the study as one of a kind.

“This is a very important paper. It defines a novel concept in cancer biology,” said cancer researcher Pinchas Cohen, professor and chief of pediatric endocrinology at the University of California, Los Angeles.

“In theory, it opens up new treatment approaches that will allow higher doses of chemotherapy. It’s a direction that’s worth pursuing in clinical

trials in humans."

Felipe Sierra, director of the Biology of Aging Program at the National Institute on Aging, said: "This is not just one more anti-cancer treatment that attacks the cancer cells. To me, that's an important conceptual difference."

Sierra was referring to decades of efforts by thousands of researchers working on "targeted delivery" of drugs to cancer cells. Study leader Longo focused instead on protecting all the other cells.

Sierra added that progress in cancer care has made patients more resilient and able to tolerate fasting, should clinical trials confirm its usefulness.

"We have passed the stage where patients arrive at the clinic in an emaciated state. Not eating for two days is not the end of the world," Sierra said.

"This could have applicability in maybe a majority of patients," said David Quinn, a practicing oncologist and medical director of USC Norris Hospital and Clinics. He predicted that many oncology groups would be eager to test the Longo group's findings, and advised patients to look for a clinical trial near home.

Longo, an anti-aging researcher who holds joint appointments in gerontology and biological sciences at USC, said that the idea of protecting healthy cells from chemotherapy may have seemed impractical to cancer researchers, because the body has many different cells that respond differently to many drugs.

"It was almost like an idea that was not even worth pursuing. In fact it had to come from the anti-aging field, because that's what we focus on:

protecting all cells at once," Longo said.

"What really was missing was a perspective of someone from the aging field to give this field a boost," UCLA's Cohen said.

The idea for the study came from the Longo group's previous research on aging in cellular systems, primarily lowly baker's yeast.

About five years ago, Longo was thinking about the genetic pathways involved both in the starvation response and in mammalian tumors.

When the pathways are silenced, starved cells go into what Longo calls a maintenance mode characterized by extreme resistance to stresses. In essence the cells are waiting out the lean period, much like hibernating animals.

But tumors by definition disobey orders to stop growing because the same genetic pathways are stuck in an "on" mode.

That could mean, Longo realized, that the starvation response might differentiate normal and cancer cells by their stress resistance, and that healthy cells might withstand much more chemotherapy than cancer cells.

The shield for healthy cells does not need to be perfect, Longo said. What matters is the difference in stress resistance between healthy and cancerous cells.

During the study, conducted both at USC and in the laboratory of Lizzia Raffaghello at Gaslini Children's Hospital in Genoa, Italy, the researchers found that current chemotherapy drugs kill as many healthy mammalian cells as cancer cells.

“(But) we reached a two to five-fold difference between normal and cancer cells, including human cells in culture. More importantly, we consistently showed that mice were highly protected while cancer cells remained sensitive,” Longo said.

If healthy human cells were just twice as resistant as cancer cells, oncologists could increase the dose or frequency of chemotherapy.

“We were able to reach a 1,000-fold differential resistance using a tumor model in baker’s yeast. If we get to just a 10-20 fold differential toxicity with human metastatic cancers, all of a sudden it’s a completely different game against cancer,” Longo said.

“Now we need to spend a lot of time talking to clinical oncologists to decide how to best proceed in the human studies.”

Edith Gralla, a research professor of chemistry at UCLA, said: “It is the sort of opposite of the magic bullet. It’s the magic shield.”

Source: University of Southern California