

Understanding Pathways of Calorie Restriction: A Way To Prevent Cancer?

By Kristina Grifantini

For decades, researchers have been intrigued by calorie restriction, a tried and true way of extending lifespans in creatures ranging from yeast and roundworms to flies and mice. Aside from increasing the lifespan of organisms up to 80% in some studies, calorie restriction (with proper nutrition) also leads to lower insulin, glucose, and blood pressure levels, as well as increased white blood cell count.

Particularly enticing is the possibility for calorie restriction to prevent, delay, and shrink a variety of tumors, a finding that seems to complement those of recent studies linking obesity and cancer. In animal studies, researchers reduce food intake by 10%–60%, but because such extreme dieting would be unrealistic in humans, many researchers are now examining the biological pathways affected by calorie restriction with the aim of developing preventive agents for cancer as well as other diseases associated with aging. Together with the growing field of calorie restriction mimetics—finding natural or synthetic compounds that mimic the effects of calorie restriction—they are finding these pathways to be numerous and complex.

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genes, pathways, and proteins that are affected in different ways,” Julie Mattison, Ph.D., a caloric restriction researcher at the National Institute on Aging (NIA), wrote in an e-mail. In gaining information about the systems changed by caloric restriction, she said, researchers can identify targets for mimetics.

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The link between cancer and caloric restriction was first suggested in the early 1900s when scientists showed that reducing caloric intake slowed the growth of transplanted tumors in mice. Since then, studies have demonstrated that caloric restriction inhibits spontaneous as well as radiation-induced tumors in mammary, prostate, and other animal models of cancer.

On a cellular level, less food intake prompts an organism to undergo a transfor-

mation. By diverting energy from reproduction and growth, the organism can focus on survival, boosting its defense system and triggering pathways that inhibit tumors. Caloric restriction also decreases cell proliferation and increases apoptosis, a combination that may slow the formation of cells inclined to turn cancerous and the proliferation of pre-existing cancer cells. Other effects include more growth of mitochondria, increased levels of the tumor suppressor p53, less DNA damage, and more active antioxidant enzymes.

Researchers are divided on which of these influences is most responsible for caloric restriction’s longevity and anticancer effects. Some are focusing on insulin-like growth factor (IGF)-1, which stimulates the cell cycle and influences the production of growth hormone, insulin, leptin, and other molecules involved with growth. Levels of IGF-1 decrease with calorie restriction, whereas its receptor, IGF-1R, is overexpressed in many tumors. Studies in vitro have shown that IGF-1 prompted growth in more than a dozen cancer lines. Others suggest that higher levels of IGF-1, in ratio to related molecules, correlate with increased risk of breast and prostate cancers.

“If you have high insulin and high IGF-1, you’re going to drive a signal through

receptors that activates a growth and survival pathway. That's exactly what cancer cells capitalize on," said Stephen Hursting, Ph.D., of the University of Texas at Austin. Hursting, who studies the effects of exercise and caloric restriction on cancer, has shown that exercise represses tumors to a lesser degree and not by decreasing IGF-1.

At the NIA, Rafael de Cabo, Ph.D., and others have focused on the NF-E2-related factor 2 (Nrf2) pathway, which activates antioxidant enzymes when triggered by caloric restriction. This pathway has been studied for years, particularly in relation to a broccoli sprout compound, sulforaphane, that inhibits tumors. In a study published in the *Proceedings of the National Academy of Sciences* in February, de Cabo and colleagues demonstrated in a chemically induced carcinogenesis model that the Nrf2 pathway is involved with caloric restriction's anticancer effects. They showed that the lack of Nrf2 increases tumor incidence in this model, even in calorie-restricted animals. A lack of Nrf2 did not affect caloric restriction's benefits on longevity and insulin signaling.

Looking to Mitochondria

Other researchers are looking to mitochondria—where damaging free radicals are produced—to explain why caloric restriction prolongs life and health. Richard Weindruch, Ph.D., at the University of Wisconsin and colleagues have shown that tissues from calorie-restricted rodents contain fewer free radicals in their mitochondria than the tissues of mice in a control group. Weindruch, who has cofounded a company called LifeGen Technologies to look for naturally occurring compounds that mimic the effects of caloric restriction, is also interested in PGC-1 α , a compound involved in oxidative stress that may be a master regulator of mitochondria.

Another team of researchers, led by Harvard pathologist David Sinclair, Ph.D., is focusing on enzymes that stimulate mitochondrial growth as caloric restriction's key mechanism. Sinclair led the well-publicized study showing that resveratrol, a chemical in red wine, had anticancer effects and helped obese mice live longer. Since

then, he and colleagues have identified the gene Sirtuin 1 (SIRT1) as a target of resveratrol and shown that a family of seven related enzymes, dubbed sirtuins, is linked to the longevity effects triggered by calorie restriction, possibly by stimulating mitochondrial growth. The continual loss of mitochondria as one grows older "is one of the reasons we think SIRT1 could be beneficial against aging," Sinclair said.

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In February, Sirtris Pharmaceuticals in Cambridge, Mass., announced results demonstrating that SIRT1 activation suppressed tumor formation and growth in an animal model of colon cancer. Details of the study should be released in the next 6 months, said Sinclair, who cofounded the company in 2004. Sirtris has partnered with the National Cancer Institute to test some recently developed synthetic molecules in cancer cell lines and multiple animal models. The molecules are chemically distinct from resveratrol but are "a thousand times more potent than resveratrol" in activating SIRT1, said the company's senior vice president, Peter Elliott, Ph.D.

In one potential new twist, some research indicates that short bouts of caloric restriction may be even more beneficial than long-term restriction, at least in normal-weight mice, according to Margot P. Cleary, Ph.D., professor at the University of Minnesota's Hormel Institute. Cleary and

colleagues have shown that this intermittent caloric restriction is more protective than chronic restriction in TRAMP mice (a model for prostate cancer), as well as in two breast-mammary tumor models. At the American Association for Cancer Research prevention meeting last December, her team reported that tumors appeared in 68% of the free-eating mice group in the mammary model and in 36% of the chronically restricted group. But only 8% of the intermittently restricted mice had tumors.

"When we did the very first experiment in 2002, we hypothesized that intermittent feeding would be bad, because when you refed you would release all of these growth factors," Cleary said. But in the latest prostate study, "we found that we were able to delay the disease detection significantly in comparison to both [free feeding] and chronic restriction." They were also able to delay death. The researchers are currently testing blood levels of IGF-1 and plan further research to see what pathways are involved.

Primate Studies

While scientists continue to detangle pathways influenced by caloric restriction, research in humans is still lacking. The only human-based studies have so far been naturally occurring and uncontrolled, based on limited data on longevity and cancer rates from Okinawans (who historically consumed fewer calories than their counterparts in the rest of Japan) and from the Dutch famine during World War II. These studies tentatively suggest that cancer occurs less frequently in calorically restricted humans.

Nonhuman primate studies, currently under way, will give researchers more clues about the effects of caloric restriction in humans. One of these, an NIA-funded study directed by Weindruch, is examining the benefits of caloric restriction on rhesus monkeys. Started in 1989, the study so far has shown that the calorie-restricted monkeys have less muscle loss and no type 2 diabetes; in contrast, diabetes has occurred in 30%–40% of the monkeys in the control group, Weindruch said. "We're seeing signs of improved health in the monkeys, including lower cancer rates," he said. About half as many of the calorie-restricted monkeys at

this point have developed cancer (colorectal) compared with the control group.

NIA's Mattison is also conducting a study on caloric restriction and longevity in monkeys, which began in 1987. Preliminary data suggest that calorie restriction does not have longevity effects when started late, she said. But so far, her restricted monkeys do have fewer cancers.

As researchers learn more about the benefits of caloric restriction and as companies start to develop synthetic molecules on the basis of their research, scientists can envision cancer-prevention agents based on multiple caloric restriction pathways. "One thing that is becoming apparent is that it's not a single pathway for all of [the caloric restriction] protective effects," de Cabo said. "Most likely it's the combination of many pathways and many different mechanisms that are involved in the [caloric restriction] response."

His colleague at NIA, Donald Ingram, Ph.D., agreed: "A cocktail approach that would hit several of these pathways may be the route to go."

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