

Research Article

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Starvation as a weapon against cancer

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Abstract

Many researchers dream about taking the approach a cut off food supply to fight cancer. As it can be known, tumors, being rapidly growing tissues, need more food than healthy cells do. Cutting off the food supply may be a good way to kill the out of control cells. While logical in theory, this approach has proved challenging in practice, because starvation harms patients too. In particular, it damages cells called tumor-infiltrating lymphocytes (TILs), that are one of the immune system's main anti-cancer weapons.

Starve a cancer but not the patient

In paper published by Cancer Cell authors are trying to craft a diet that weakens tumors, while simultaneously sneaking vital nutrients to healthy tissues, TILs included. Team of Dr Longo of the University of Southern California in Los Angeles, first used starvation as a weapon against cancer in 2012. In experiments on mice, they employed starvation in parallel with doxorubicin, a common anticancer drug. This combination resulted in the animals' tumors shrinking by an average of four-fifths, as opposed to a half if they were dosed with the drug alone.

The question was the researchers may mimic the benefits of starvation while minimising its problems in humans. The result is a diet rich in vitamin D, zinc, fatty acids essential to TILs' performance, while the diet must be low in the proteins and simple sugars that tumors make ready use of.

The test of this type of diet efficacy included injection to mice with breast-cancer cells. For the first two days after the injections they fed these mice standard rodent chow, composed of 25% protein, 17% fat and 58% simple sugars and complex vegetable carbohydrates. This contained 3.75 kilocalories per gram. They then put ten of the animals onto a transition diet. Besides its special ingredients consist of 0.5% protein, 0.5% fat and 99% complex carbohydrates that would be of little value to cancer cells.

After experiment the team found that both the rodents which had been starved and those which had been fed the special diet developed tumors which were only two-fifths of the size of those found in the mice on the ordinary diet. Later run the experiment again, but with the addition of doxorubicin. The results were impressive. In combination with special diet, doxorubicin drove

tumors down to a quarter of the size of those found in control mice, close to the reduction achieved in 2012.

To work out what was happening at the cellular level, researchers collected samples of breast-cancer tissue from the mice in the re-run experiment and scanned these for TILs. They found that, while such cells were indeed present in the tumors of mice fed ordinary chow, there were 70% more of them in the tumors of mice given doxorubicin alone, 80% more in those mice that were on the special diet alone and 240% more TILs in mice that had been given both therapies.

A follow-up experiment revealed at least part of what was going on. An enzyme called haeme oxygenase- 1, which helps regulate immune responses, turned out to be protecting tumors from the attention of TILs in mice on the normal diet. Dr Longo's diet seems to suppress above enzyme's production in a tumor, and that encourages TILs to accumulate. Add in the drug, and the tumor faces a two-pronged assault. Further work by the team suggests this approach also works on melanoma, an aggressive form of skin cancer. A siege mentality can pay off. (Longo et al., 2016)

Humans are able to fight cancer with their own immune system

Human bodies are constantly and successfully fighting off the development of cells that lead to tumors. When there is a disruption to this process cancer is free to develop. Researchers are investigating the ways to 'switch on' our Natural Killer (NK) cells. These cells exist to detect and then destroy any deviant cells in human bodies before those cells go on to develop into tumors

or before infection spreads. Natural Killer cells are a key part of the human immune system that locate other cells posing a danger to health either because they are infected or because they are becoming a cancer cell.

It is known that abnormal cells sometimes escape the immune system and develop into a cancer. The researchers identified a ‚protein brake‘ within Natural Killer cells that controls their ability to destroy their target tumor cells. In their paper published in May 2016 in *Nature Immunology*, they showed that when the brake was removed in an experimental model, the NK cells were better able to protect the body against metastatic melanoma.

Natural Killer cells rely on a growth factor called Interleukin 15 (IL 15) to activate. Research has shown that an inhibitor protein made inside the NK cells limits the ability of the NK cells to respond to IL 15 and therefore kill cancer cells. After identifying for the first time how this protein inhibits NK cell responses, researchers now hope that a drug can be developed that will improve the NK cells‘ response to this growth factor and help patients fight cancer with their own immune system.

This is about learning how to activate the NK cells of the individual patient and boost their immune system to tackle the disease. Research may lead to new immunotherapies that supercharge the body’s Natural Killer cell and maintain it in a highly active state to more efficiently and specifically fight cancer. (Nicholson & Huntington, 2016)

Bacteria may assist the immune system response against cancer

Researchers have shown that various types of intestinal bacteria might be factors in both causing and preventing obesity, and in other conditions and diseases. Now, a UCLA study suggests that it could also potentially be used to reduce the risk for some types of cancer. The research, published online April 13 in a peer-reviewed journal *PLOS ONE*, offers evidence that anti-inflammatory ‚health beneficial‘ gut bacteria can slow or stop the development of some types of cancer.

It is possible to reduce a person’s risk for cancer by analyzing the levels and types of intestinal bacteria in the organism, and then prescribing probiotics to replace or bolster the amount of bacteria with anti-inflammatory properties. It is not invasive and rather easy to do. Over millions of years, gut bacteria have developed into both good and bad types: The good ones have anti-inflammatory properties and the bad ones promote inflammation. The human body typically contains about 10 trillion bacterial cells, compared with only 1 trillion human cells.

Schiestl and his colleagues isolated a bacterium called *Lactobacillus johnsonii* 456, which is the most abundant of the beneficial bacteria, and which has some useful applications outside of medicine. As a *Lactobacillus* strain, it makes excellent yogurt, kefir, kombucha and sauerkraut. In the UCLA study the bacterium reduced gene damage and significantly reduced inflammation, a critical goal because inflammation plays a key role in many diseases, including cancer, neurodegenerative disease, arthritis and

lupus, and the aging process.

Previous research led by Schiestl presented the first evidence of relationship between intestinal microbiota and the onset of lymphoma, a cancer that originates in the immune system. The new study explains how this microbiota might delay the onset of cancer, and suggests that probiotic supplements could help keep cancer from forming.

For both studies, Schiestl and his team used mice that had mutations in a gene called ATM, which made them susceptible to a neurologic disorder called ataxia telangiectasia. The disorder affects 1 in 100,000 people, is associated with high incidence of leukemia, lymphomas and other cancers.

In the *Cancer Research* paper, Schiestl and his team showed that in the mice with more of the beneficial bacteria, the lymphoma took significantly longer to form. In the new study, the researchers analyzed the metabolites, molecules produced by the gut’s natural metabolic action in the mice’s urine and feces. They find that the mice that were receiving only the beneficial microbiota produced metabolites that are known to prevent cancer. Those mice had also more efficient fat and oxidative metabolism, which the researchers believe might also lower the risk for cancer.

Among the other results, in the mice receiving only the good bacteria, lymphoma formed only half as quickly as it did in the other mice. In addition, mice with the good bacteria lived four times longer and had less DNA damage and inflammation. These findings lend credence to the notion that manipulating microbial composition could be used as an effective strategy to prevent or alleviate cancer susceptibility. Their findings suggest that composition of the gut microbiota influence and alter central carbon metabolism in a genotype independent manner. The use of probiotics-containing supplements would be a potential chemopreventive for normal humans, while the same type of microbiota would decrease tumor incidence in cancer susceptible populations. (Schiestl et al., 2016, Bullwinkle et al., 2016)

UCLA has a patent pending on the use of *Lactobacillus johnsonii* 456 as an anti-inflammatory agent.

Microbiome can mean the difference between life and death in cancer

Development in microbiome sequencing techniques are today leading to a personalized therapies for a number of diseases. The trillions of bacteria in our gut are critical for a wide range of key functions. While many are aware that our microbiota is important for digestion, it is now known that it also plays a key role in our immune system. The gut microbiota consists of up to 2,000 different species of bacteria as well as other kinds of microbes, including parasites and viruses.

Mapping the microbiome is critical to maintaining good health. Millions of people today regularly consume food-based probiotics and probiotic supplements without any map of their current bacteria. People eat yogurt, drink kombucha, and consume other fermented foods in the hopes of improving their internal flora. It

makes more sense to first map each patient's microbiome to assess where they are lacking and only then carefully choose a proper supplement or eat certain bacteria-rich foods.

Microorganisms in the gut can be used to empower the immune system to fight cancer, as opposed to traditional therapies that dramatically weaken it. Perhaps the most astonishing aspect of the microbiota is its control over the immune system. Particular species of bacteria have been identified for their ability to upregulate the activity of antigen-presenting cells (APCs). Without properly functioning APCs, the immune system cannot respond to threats, whether it be a virus or tumor. When they are doing their job, APCs are able to bring the threat to the attention of B and T-cells, which initiate a chain of events to attack and eradicate the threat. The observation that Bifidobacterium, many strains of which are found in the gut, are able to increase the activity of APCs, has the potential to change the way treatment of cancer and other diseases is approached.

As with all systems of the body, balance is key. In the immune system, there is a checkpoint that stops the T-cells from overdoing it. Unfortunately, many cancer cells are able to take advantage of this mechanism to shut down the T-cell activity before the job is done. After a decade of research, a therapy was developed to prevent tumor cells from cheating the system. The therapy has been shown to improve the activity of T-cells in up to 35% of patients with melanoma (a form of skin cancer). A study published in Science reported that combining this checkpoint blockade therapy with supplements of Bifidobacterium could produce a much stronger immune response to tumor cells.

The University of Chicago research team found that variations in intestinal microbiota affected the growth of melanoma in mice. Mice who received an oral supplement of Bifidobacterium improved tumor control to the same degree as those who received the checkpoint blockade therapy, in comparison with the minimal tumor control exhibited by mice receiving neither. When mice were treated with both Bifidobacterium and checkpoint blockade therapy, tumor outgrowth was almost completely abolished !

This treatment involves no chemotherapy or radiation, instead, it empowers the natural mechanisms already present in the immune system using antibody therapy and a commercially available Bifidobacterium supplement to increase the activity of the APCs. The Bifidobacterium supplement used in the Science study to treat melanoma can be purchased for a mere \$42 a bottle.

This holds the promise of increasing the efficacy of anti-PD1 checkpoint inhibition immunotherapy, which currently is only effective for 25-35% of patients for a durable response. There are reports of greater numbers with combination of a CTLA4-blocker and anti-PD1 but this is a difficult treatments with very high probabilities of toxic side effects. If we can increase the durable response of anti-PD1 therapy to 65% of patients, we will the face of cancer treatment.

In addition to cancer, it is becoming well known that the bacteria in your gut have a big effect on the digestion system. Irritable bowel

syndrome (IBS), is a disorder of the gut that affects about one out of ten people in the world. C. diff, a disease named for the bacteria causing it, is an infection causing a wide variety of potentially life-threatening problems in the gut. Since these diseases are associated with an imbalance of bacteria in the gut microbiota, fecal matter transplants (FMTs) can treat the condition by reintroducing a healthy assortment of bacteria to the gut. As with probiotics, sequencing the microbiome would allow for a more patient-specific therapy directed at that problem. This same approach could be applied to the treatment of any number of diseases, completely changing the way we think about individualized therapy. We must also cover the human virome (the collection of all viruses resident in our bodies), some dormant for years. The new approach to the microbiome and virome will change medicine as we know it. (Sivan & Corrales et al., 2015)

The link between altered gut microbes and changes in appetite and eating behaviors

A new study suggests altering the makeup of gut microbes could be an effective way to address obesity and related problems. This is the first study to specifically identify the mechanism by which changes in patient's gut microbes influences the likelihood for developing obesity and metabolic syndrome, a cluster of conditions that include high blood pressure, high blood sugar, excess body fat around the waist and abnormal cholesterol levels.

In studies on mice, researchers at the Yale University School of Medicine found that acetate, a short-chain fatty acid, is responsible for modulating the production of insulin in rodents. They compared the effects of acetate and other short-chain fatty acids and discovered that the mice with higher levels of acetate were more likely to consume a high fat diet. The researchers then infused acetate into a group of rodents to see whether it would cause the animals to put on weight. Injected the rodents with acetate stimulated insulin secretion by the pancreas. Higher level of insulin increases the storage of fat and prevents the body from releasing it for energy production.

Next, they injected acetate directly into brains of these rodents. This caused an increase in insulin production and stimulated the secretion of gastrin and ghrelin, two hormones that are known to increase food intake. To identify the link between altered gut microbes and changes in appetite and eating behaviors, the researchers transferred fecal matter from group of obese rodents to healthy rodents. That caused changes in the gut microbes of the healthy mice, and changes in acetate and insulin levels that could result in obesity.

Last year, the journal Open Forum Diseases published a case study of patient treated for C. difficile infection with fecal transplantation. Transplanting healthy stool, either through capsules or colonoscopy, has more than a 90% success rate for clearing C. difficile infections. Her BMI rose from 26 to 33 in little over a year after the transplant. Physicians suspected the fecal transplant was most likely the cause of her weight gain, thereby showing the bugs in the gut may very well determine the girth of one's belly. (Alang & Kelly, 2014)

Block the metabolism of L-glutamine – the tumors stopped growing

Researchers in the USA have discovered that reducing the amount of the L-glutamine amino acid in the body can block the growth of colorectal cancer tumors in mice. The first clinical trials on humans are due to begin this summer.

L-glutamine is a non-essential amino acid found in eggs, meat, fish, dairy products, cereals and pulses. It is also found in raw spinach and parsley, as well as Asian miso. It's recommended as a dietary supplement, for reducing intestinal permeability. Recent research has established that cancerous tumors rely on L-glutamine to survive and grow.

In this latest study, researchers found that a subset of colorectal cancer containing a genetic mutation called PIK3CA (a commonly occurring mutation in cancer cells) were particularly high consumers of L-glutamine when growing. When Professor Zhenghe John Wang and his team reduced the amount of L-glutamine available to these mutant cancer cells growing in laboratory dishes, the cells died.

This discovery, outlined in the journal *Nature Communications*, inspired the scientists to investigate the effects of depriving the cells of L-glutamine in mice with colorectal cancer tumors. They found that when mice were given a compound to block the metabolism of L-glutamine, the tumors stopped growing. This effect was not seen in tumors that did not contain the PIK3CA mutation.

The findings, which are currently the subject of a patent application, could lead to the development of a new drug to suppress tumor growth. The first clinical trials of an L-glutamine inhibitor in human patients with advanced stage colorectal cancer will begin this summer. (Yujun Hao et al., 2016)

The parasite secretes direct the immune system to attack tumors

Research on the parasite *Toxoplasma gondii* (*T. gondii*), commonly found in cat feces, reveals how nasty and widespread it is. It's linked to the rage disorder, might boost one's risk of schizophrenia and other mental disorders. In an odd and probably fatal twist makes the mice it infects no longer fears cats.

New research out of Dartmouth's Geisel School of Medicine suggests that, at least in mice, it has a major upside: The parasite secretes specific protein that directs its immune system to attack ovarian tumors, researchers report in the journal *PLOS Genetics*. They built upon previous research to produce a vaccine that's a safe strain of *T. gondii*, one that could cure mice of multiple types of solid tumors, not just ovarian.

Ovarian cancer usually isn't detected until it has metastasized (it has spread to other tissues and organs). As a result, it accounts for the fifth-most cancer deaths among women, claiming more than 14,000 lives a year, per the American Cancer Society. Researchers note that clinical trials are already underway exploring the use of the bacterium *Listeria monocytogenes* to break the body's immune

tolerance of pancreatic tumors and essentially whip the immune system in the attack mode. *T. gondii* could work in a strikingly similar way. What works in mice doesn't always in humans, there is a hope to develop therapies that attack the most aggressive tumors. The Holy Grail of the ovarian cancer may be near. (Fox et al., 2016)

Kamikaze Bacteria Attack Deep Tumors

In mice, microbes released anticancer toxin that, with chemotherapy, shrank tumors. Bacteria have been engineered to manufacture anti-cancer drugs and self-destruct to spill this cargo deep inside tumors. In combination with chemotherapy, the approach shrank a tumor in a mouse model for liver cancer more than chemotherapy alone.

To create the cancer therapy, University of California, San Diego researchers turned to *Salmonella* as this bacterium likes to colonise tumors as a way of hiding from the body's immune system. The bacterium was engineered to produce the toxin haemolysin, along with a chemokine to call in the host's own defences. A 'kill switch' was also design into them that would cause the cells to break open when flipped.

When tested in a mouse model of liver cancer, the bacteria did not perform better than chemotherapy alone, but in combination there was a significant effect. For the combined therapy the researchers observed decreases in tumor size and 50% increase in life expectancy in mice with metastatic cancer. Think of the bacteria as an army that enters behind enemy lines, to the interior of the tumor, which is where chemotherapy finds it hard to reach. The group previously reported that orally delivered engineered *Escherichia coli* colonise liver tumor tissue but not healthy organs.

The simultaneous self-destruction of the bacteria is under the control of a small signaling molecule, AHL, which flows in and out of the cells. Its introduction is stimulated by the presence of AHL so as the bacterial colony grows levels of the molecule rise. Once the concentration of AHL passes the threshold, a protein is produced that obliterates the bacteria's cell wall releasing its deadly cargo.

Once the density of *Salmonella* in the tumor reaches a few thousand bacterial cells, the self-destruction switch is tripped, releasing more anti-cancer drugs and killing off 90% of the bacteria. The 10% of the bacteria that survive regrow the population. This cycle of growth, self-destruction and drug release continues.

The bacteria lose their ability to deliver drugs after about 18 days, but oral administration means it is easy to take another dose. Researchers are modifying bacteria so that they kill any remaining bacteria from a previous dose, in addition to cancer cells, so that they wipe the slate clean.

An advantage with this approach is that the bacteria synchronously lyse and so their population shrinks. That is a safety mechanism. This restricts the bacterial population to a defined size, which minimizes the risk of an adverse systemic inflammatory response in a patient. This changes our thinking about how to engineer

bacteria. It is also a first and more combinations of potent therapeutics can be now tested. (Omar Din et al., 2016)

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