

## Winning the War on Cancer

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### Abstract

*A new study has uncovered how brain injury can be worsened by bacteria in the gut. The gut-brain connection is one of the more fascinating new areas of medical research. This intriguing two-way axis has been found to have numerous unexpected effects. On one hand some studies have demonstrated how magnetic brain stimulation can alter person's gut microbiome while other studies have shown how gut bacteria could potentially play a role in the onset of PTSD (post traumatic stress syndrome) and Alzheimer's. Studies in patients and subsequent mouse research really drive home that our gut microbiomes modulate both systemic and anti-tumor immunity, said Jennifer Wargo, a surgical oncologist and geneticist at the University of Texas MD Anderson Cancer Center. She is planning clinical trials to see if fecal transplant in cancer patients could improve immunotherapy success rates. The main conclusion from this is: You can change your microbiome.*

**Keywords:** Brain injury, bacteria, the gut-brain connection, gut microbiome, two-way axis, blood poisoning, microbial priming, checkpoint inhibitor, the Warburg effect, glucose, glycolysis.

### Brain injury can be worsened by bacteria in the gut

A new study from the University of Maryland School of Medicine has revealed another strange gut-brain connection, this time between traumatic brain injury (TBI) and intestinal damage. Researchers have previously identified an odd connection between TBI and alterations in person's gastrointestinal tract, but this is the first study to understand this interaction in detail and reveal the two-way nature of the process.

The study looked at mice that were subjected to TBI, and discovered that following the brain trauma, the animal's colon became more permeable. This means that bacteria can more easily move to other areas in the body, resulting in potentially fatal scenarios such as blood poisoning.

The team also looked at how irregularities in the gut could affect inflammation in the brain after TBI. In this instance, after infecting TBI-inflicted mice with negative gut bacteria, the animal's brain inflammation was seen to worsen. This fascinating result suggests that the harmful effects of TBI can be directly influenced by gut dysfunction.

These results indicate strong two-way interactions between the brain and the gut that may help explain the increased incidence of systemic infections after brain trauma and allow new treatments approaches, says researcher Alan Faden.

The study helps explain why patients suffering from TBI have been two and half times more likely to die from digestive problems than a person not afflicted by brain injury. The mechanism that is causing this strange interaction is yet unknown, but this is strong research affirming the complexity of above two-way connection between the gut and the brain [1].

### Gut bacteria make or break your chances of cancer treatment

New, potent cancer therapies can act like daggers pressed into hindquarters of the immune system, prodding it to lunge at any cancerous cells in the body. When the drugs work, the immune system tramples tumors into oblivion. But they not always work – in fact, cancer drugs can fail 60 to 70 percent of the time. The drugs might not give the immune system a sharp enough sticking in every patient. But according to a pair of new studies, it may not be the immune system that needs a swift kick – it may be the gut.

Some intestinal-dwelling bacteria appear to corral and train immune cells to fight off cancer cells – prior to any spurring from cancer immunotherapies. Without such microbial priming, the drugs may only offer a futile prod. In both studies, published in Science, researchers found that the cancer patients who saw no benefit from the drugs (non-responders) were the ones who lacked certain beneficial gut bugs, particularly after taking antibiotics. Cancer patients who did respond to the drugs had bacteria that could prompt the immune system to release chemicals that get cancer-killing immune cells – T cells – to chomp at the bit.

When the researchers transferred the gut microbes from their human cancer patients into germ-free mice with cancer, the rodents mirrored the patients fates. That is, mice that got gut microbes from non-

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responding humans also did not respond to immunotherapies. But, that got microbes from responders responded. When researchers swapped responder gut microbes into non-responding mice, the mice converted and fought back the cancer.

Custom cancer vaccines safely fight and kill tumors in early human trials. In Dr. Vargo's study and in other – led by immunologist Laurence Zitvogel of the Gustave Roussy Cancer Campus in Villejuif, France – researchers focused on a type of checkpoint inhibitor cancer treatment called PD-1 inhibitors. Generally, PD-1 is a protein on the surface of the T cells that-in non-cancerous scenarios – acts as a checkpoint to guard against over-zealous immune responses and auto-immune diseases. PD-1 does this by latching onto proteins on healthy cells, namely PD-L1, which basically signals to the T cell to stand down and not attack the healthy cell.

Crafty cancer cells often don PD-L1, though, allowing them to escape a T cell blitz. That's where the PD-1 inhibitors come in. If the drugs get in the way of PD-1 binding to PD-L1 on cancer cells, they can help unleash the wrath of T cells on those tumors. But, as mentioned, PD-1 inhibitor therapies often don't work.

Prior to the new study, Zitvogel and colleagues noticed that recent mouse studies were showing that gut microbes play a role in regulating immune responses to cancers. They hypothesized, the bacteria-killing antibiotics could squash the effects of PD-1 inhibitors. To see of that held up, they simply looked at the outcomes of 249 patients with either lung, kidney, or bladder cancer, some of whom received antibiotics around the time of their PD-1 inhibitor treatments. The researchers found a clear link between antibiotic use and immunotherapy failures. Specifically, the 69 patients taking antibiotics had shorter survival times and periods without their cancer progressing compared with patients with the same cancers and similar health factors.

Next, the researchers examined the communities of microbes in the poop of 100 responding and non-responding cancer patients. They found big differences in the abundance of certain types of bacteria. Specifically, those who responded to PD-1 inhibitors were more likely to carry *Akkermansia muciniphila*, an intestinal bacterium hypothesized to have anti-inflammatory effects. In mouse experiments, *A. muciniphila* spurred immune cells to release a chemical signal called IL-2, which is known to regulate T-cells and prime them to attack. Likewise, treatments of *A. muciniphila* could convert non-responding gut microbes into responding microbes in mice with cancer.

Wargo's study had similar findings. In their work with 112 skin cancer patients undergoing PD-1 inhibitor treatments, they, too, found that patient's gut microbiomes is linked with the success or failure of their immunotherapy. Though they didn't pick out *A. muciniphila* specifically, they noted that responders tended to have more diverse communities and more of certain types of bacteria. When they transferred the patients' gut microbiomes into germ-free mice with cancer, the mice met the same fate as their human microbe donors. The researchers also found evidence of beneficial microbes priming T cells.

Together, the studies suggest a big role for gut microbes in determining the cancer-killing potential of immunotherapies. But there are still plenty of questions, namely how exactly, certain

bacteria may spure the immune system to fight cancer and if there are side-effects or potential dangers of manipulating the microbiomes of cancer patients.

These findings highlight the therapeutic potential of modulating the gut microbiome in patients receiving checkpoint blockade immunotherapy, and they warrant prompt evaluation in cancer patients through clinical trials [2,3].

#### **A new way to shut down cancer cell's ability to consume glucose**

Joaquin Espinoza, PhD, Mathew Galbraith, PhD, and university of Colorado Cancer Center colleagues demonstrate link between gene CDK8 and the ability of cancer to uptake and metabolize glucose. Cancer cells consume exorbitant amounts of glucose, a key source of energy, and shutting down this glucose consumption has long been considered a logical therapeutic strategy.

Good pharmacological targets to stop cancer's ability to uptake and metabolize glucose are missing. In a new study published in *Cell Reports*, a team of University of Colorado Cancer Center researchers, led by M. Galbraith and J. Espinoza finally identifies a way to restrict the ability of cancer to use glucose for energy.

Over-expression of the gene CDK8 is linked to the development of many cancers including colorectal cancer, melanoma, and breast cancer, where it regulates pathways that drive the growth and survival of cancer cells. Although a number of drugs aimed at blocking CDK8 activity are currently being developed, it is not yet clear how effective they are at treating various cancers. Galbraith and Espinoza have been working to better understand the role of CDK8 in cancer biology in the hopes of aiding the introduction of CDK8-based therapies as cancer treatments [4].

Their recent study, which was funded in part by the Cancer League of Colorado demonstrates that CDK8 plays a critical role in allowing cancer cells to use glucose as an energy source. The finding takes place against the backdrop of the tissue conditions in which tumors grow, as cancer cells rapidly multiply, their growth often outstrips their body supply, leading to depletion of oxygen (i. e. hypoxia) and other nutrients such as glucose. In 2013, the group published paper showing that CDK8 is important for activation of many genes switched on in hypoxic conditions. During adaptation to these conditions, cancer cells must alter their metabolism to consume more glucose through a process of glycolysis. In fact, many cancer cells have permanent increases in glycolysis, maintained even in conditions of plentiful oxygen, a phenomenon known as the Warburg effect, which was described as far back as 1924. Consequently, many cancers are heavily dependent on glucose metabolism for their growth and survival. This is true to the point that doctors use glucose isotopes and PET scans to pinpoint the exact location of a tumor and its metastases within human body – where there are abnormally high levels of glucose being used, chances are there is a cancerous growth.

When Galbraith used a sophisticated chemical genetics approach to specifically switch off CDK8 activity in colorectal cancer cells, he saw that the cells failed to activate glycolysis genes and took up less glucose. He confirmed this in experiments showing that blocking CDK8 activity leads to a lower rate of glucose use.

Because of this role of CDK8 in glycolysis, he reasoned that the

cells with impaired CDK8 activity should be more susceptible to drugs that block glycolysis. Sure enough, treating cancer cells with drugs that block both CDK8 and glycolysis slowed their growth more effectively than either approach alone.

These are very exciting discoveries. The Warburg effect and consequent addiction to glucose is a hallmark of cancerous tissues, something that distinguishes cancer cell from most normal tissues. Therefore, combining drugs that block CDK8 activity with those that block glycolysis may enable specific targeting of cancer cells without harmful effects on normal cells [5].

### Relationship between sugar and cancer

A nine-year joint research project conducted by VIB, KU Leuven and VUB has led to a crucial breakthrough in cancer research. Researchers have clarified how the Warburg effect, a phenomenon in which cancer cells rapidly break down sugars, stimulates tumor growth. This discovery provides evidence for a positive correlation between sugar and cancer, which may have far-reaching impacts on tailor-made diets for cancer patients. The research has been published in the leading academic journal *Nature Communications*.

This project was started in 2008 under the leadership of Johan Thevelein (VIB-KU Leuven), Wim Versees (VIB-VUB) and Veerle Jansens (KU Leuven).

Its main focus was the Warburg effect, or the observation that tumors convert significantly higher amounts of sugar into lactate, compared to healthy tissues. As one of the most prominent features of cancer cells, this phenomenon has been extensively studied and even used to detect brain tumors, among other applications. But thus far, it has been unclear whether the effect is merely a symptom of cancer, or a cause.

While earlier research into cancer cell metabolism focused on mapping out metabolic peculiarities, this study clarifies the link between metabolic deviation and oncogenic potency in cancerous cells.

Their research reveals how hyperactive sugar consumption of cancerous cells lead to a vicious cycle of continued stimulation of cancer development and growth. Thus, it is able to explain the correlation between the strength of the Warburg effect and tumor aggressiveness. This link between cancer and sugar has sweeping consequences.

### Yeast as a model organism

Yeast cell research was essential to the discovery, as these cells contain the same Ras proteins commonly found in tumor cells, which cause cancer in mutated form. Using yeast as a model organism, the research team examined the connection between Ras activity and the highly active sugar metabolism in yeast.

Researchers observed in yeast that sugar degradation is linked via the intermediate fructose 1,6-bisphosphate to the activation of Ras proteins, which stimulate the multiplication of both yeast and cancer cells. It is striking that this mechanism has been conserved throughout the long evolution of yeast cell to human.

However, the findings are not sufficient to identify the primary cause of the Warburg effect. Further research is needed to find out whether this primary cause is also conserved in yeast cells [6].

### The best diet according to Harvard researchers

If you want to lose weight, what's on your plate is often more important than the minutes you spend in the gym. And if you want to see the most change, a study from Harvard says that you should be cutting carbohydrates (carb), not only fat.

For the study, published in journal *PloS One*, researchers from Harvard and Brigham and Women's Hospital reviewed 53 randomized trials of over 68,000 patients who had been assigned to either low-fat or low-carb diets. They found that low-carb diets were consistently better at helping patients lose weight than low-fat diets. The participants on the low-carb diets lost 2.5 pounds more than those on low-fat diets, with an average weight loss among all groups at about 6 pounds.

Another study on the weight-loss benefits of a low-carb diet adds further evidence that if you want to lose weight, ditching bread – not olive oil – can help you see success. Another recent study also showed that dieters who ate fewer than 40 grams of carbohydrates per day lost about 8 pounds more than dieters who were put on a low-fat diet.

Several other studies have shown that high-carb diets may be the real heart-disease culprit, not only saturated fat [7].

All in all, this new review is a good reminder that if you want to lose weight, you should choose a diet in healthy fats, lean proteins, and fresh produce. Of course, not all fats are created equal – you must find out which healthy fats are recommended by science to be incorporating into your diet [8].

Our cells are coated with sugar, and when it comes to cancer, that's anything but sweet. In a recent talk at TEDx Stanford, chemical Carolyn Bertozzi explained why. She studies sialic acid, a sugar that seems to deceive the immune system, allowing cancer cells to evade the body's defenses. This work focuses on the complex, sugary structures surrounding human cells. That foliage-like coating, it turns out, can tell us a lot of our body – it even reveals a patient's blood type. Sugar and carbohydrates are a dangerous supporters of different types of cancer.

### Sugar, carbs and cancer links

In August of 2016, the *New England Journal of Medicine* published a striking report on cancer and body fat: Thirteen separate cancers can now be linked to being overweight or obese, among them a number of the most common and deadly cancers of all - colon, thyroid, ovarian, uterine, pancreatic and (in postmenopausal women) breast cancer. In November 2017 a report from the Centers for Disease Control and Prevention added more detail: Approximately 631,000 Americans were diagnosed with a body fat-related cancer in 2014, accounting for 40 percent of all cancers diagnosed that year [9].

Increasingly, it seems not only that we are losing the war on cancer, but that we are losing it to what we eat and drink. It is a warning sign that something about what or how we eat is intimately linked to cancer.

Lewis Cantley, the director of the Cancer Center at Weil Cornell Medicine, has been at the forefront of the cancer metabolism revival. His best explanation for the obesity-cancer connection is that both conditions are also linked to elevated levels of the hormone insulin.

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His research has revealed how insulin drives cells to grow and take up glucose by activating a series of genes, a pathway that has been implicated in most human cancers.

The problem is not the presence of insulin in our blood. We all need insulin to live. But when insulin rises to abnormally high levels and remains elevated (a condition known as insulin resistance, common in obesity), it can promote the growth of tumors directly and indirectly.

Too much insulin and many of our tissues are bombarded with more growth signals and more fuels than they would ever see under normal metabolic conditions. And because elevated insulin directs our bodies to store fat, it can also be linked to the various ways the fat tissue itself is thought to contribute to cancer.

Having recognized the risks of excess insuli-signaling, Cantley and other metabolism researchers are following the science to its logical conclusion: The danger may not be simply eating too much, as is commonly thought, but rather eating too much of specific foods most likely to lead to elevated insulin levels – easily digestible carbohydrates in general, and sugar in particular.

This is not say that all cancers are caused by too much insulin or that we should never eat sugar again. Michael Pollak, a metabolism researcher and director of cancer prevention at McGill University in Canada, says that the best approach to sugar is think of it like a spice – something to occasionally sprinkle on foods, as opposed to an ingredient in nearly every meal and too many drinks.

Nutrition is an inherently messy science. But recent advances in cancer metabolism research are sending as an increasingly clear message about our diet. Winning the war on cancer may depend upon whether we're ready to hear it [10].

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