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WEIZMANN INSTITUTE OF SCIENCE
Science Tips

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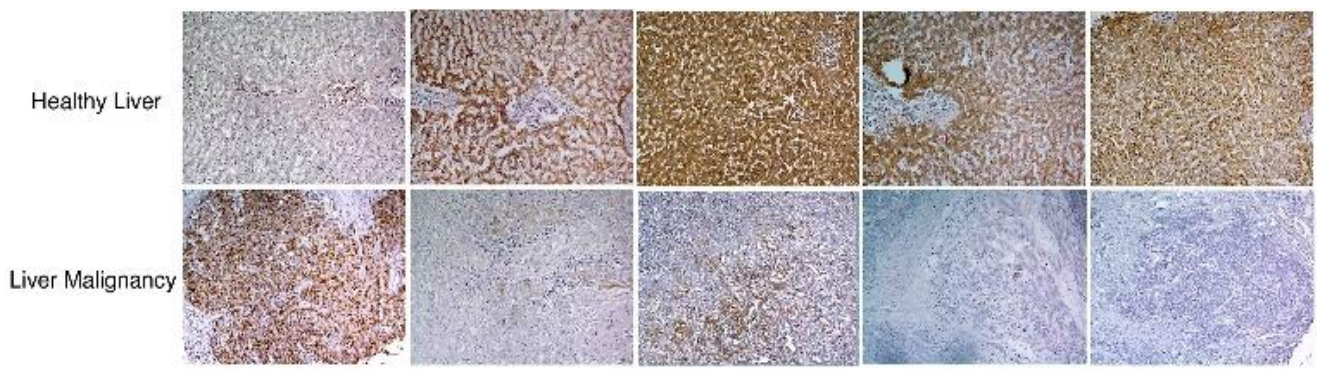
Disrupted Nitrogen Metabolism Might Spell Cancer



Staining of normal liver tissue (upper row, four images from right) reveals high levels of four different urea cycle enzymes (brown or reddish-brown), whereas liver cancer samples (bottom row, four images from right) have low levels of these enzymes. In In contrast, markers for cell growth are low in the normal tissue (upper row, left) and extremely high in the liver cancer (bottom row, left). Image generated with the help of Dr. Raya Eilam

Nitrogen is a basic building block of all the body's proteins, RNA and DNA, so cancerous tumors are greedy for this element. Researchers at the Weizmann Institute of Science, in collaboration with colleagues from the National Cancer Institute and elsewhere, have now shown that in many cancers, the patient's nitrogen metabolism is altered, producing detectable changes in the body fluids and contributing to the emergence of new mutations in cancerous tissue. The study's findings, published recently in *Cell*, may in the future facilitate early detection of cancer and help predict the success of immunotherapy.

When the body makes use of nitrogen, it generates from the leftovers a nitrogenous waste substance called urea in a chain of biochemical reactions that take place in the liver, which are known as the urea cycle. As a result of this cycle, urea is expelled into the bloodstream, and is later excreted from the body in the urine. In previous research, Dr. Ayelet Erez of Weizmann's Biological Regulation Department showed that one of the enzymes in the urea cycle has been inactivated within many cancerous tumors, increasing the availability of nitrogen for the synthesis of an organic substance called pyrimidine, which, in turn, supports RNA and DNA synthesis and cancerous growth.

In the new study, conducted with Prof. Eytan Ruppin of the National Cancer Institute and other researchers, Erez's team identified a number of precisely defined alterations in additional enzymes of the urea cycle, which together increase the availability of nitrogenous compounds for pyrimidine synthesis. These alterations lead to increased pyrimidine levels in the tumor and predispose the cancer to mutations.

When the researchers made changes in the expression of urea cycle enzymes within colon cancer tumors in mice, these mice – in contrast to the control group – had lower urea levels in the blood as well as detectable pyrimidine levels in the urine. Next, the researchers surveyed the medical records of 100 pediatric cancer patients treated at Tel Aviv Sourasky Medical Center to check for their urea levels. "We found that on the day of their admission to the hospital, children with cancer had significantly decreased urea levels in their blood, compared with documented levels of urea in healthy children of the same age," Erez says.

These findings suggest that dysregulation of the urea cycle in the liver and in tumors may lead to generation of nitrogen-related markers that will facilitate early detection of cancer. Future tests may rely on a score that will combine measurements of urea levels in blood, and of pyrimidine in urine, to sound an alarm that cancer may be lurking in the body.

"Standard laboratory tests check for high levels of urea in blood, but we are now showing that low levels can also signal a problem," Erez says. "Cancerous cells don't waste anything, they make use of as much nitrogen as possible instead of disposing of it in the form of urea, as do normal cells."

Furthermore, after examining large sets of genomic data on cancer, the researchers discovered that dysregulation of the urea cycle is prevalent in many cancer types, and that it is accompanied by specific mutations resulting from the increased synthesis of pyrimidine.

These pyrimidine-related mutations are a double-edged sword. On the one hand, they render the cancer more aggressive, reducing patients' survival, but they also generate protein fragments that make the tumor more "sensitive" than average to the impact of the immune system. Therefore, tumors with a dysregulated urea cycle are more likely to be susceptible to immunotherapy, in which the patient's own immune mechanisms are directed at fighting the tumor. An analysis of patients with melanoma indeed revealed that those with tumors characterized by dysregulated urea cycle enzymes were more likely to respond to immunotherapy than those without these characteristics. When the researchers induced dysregulation of the urea cycle enzymes in cancerous tumors in mice, they found that these mice responded much better to immunotherapy than those carrying tumors with an intact activity of the same enzymes.

If these findings are confirmed in larger studies in animals and humans, they may lead to a test that will help evaluate the chances of immunotherapy's success based on biopsy staining, rather than on a genomic analysis that is much more complicated to perform. Dysregulation in the expression levels of urea enzymes in the tumor tissue would suggest that the patient is more likely to respond to immunotherapy.

"Yet another possibility worth exploring is whether genetic manipulation of the tumor to induce such dysregulation prior to immunotherapy can increase the therapy's effectiveness," Erez says. This manipulation would involve deliberately disrupting the tumor urea cycle in the hope that this disturbance generates pyrimidine-related mutations in proteins, helping the immune system to identify and destroy the tumor.

Study participants included Dr. Lital Adler, Dr. Narin Carmel, Shiran Rabinovich, Dr. Rom Keshet, Dr. Noa Stettner, Dr. Alon Silberman, Hila Weiss and Sivan Pinto of Biological Regulation Department, Dr. Lilach Agemy and Prof. Avigdor Scherz of Plant and Environmental Sciences Department, Dr. Raya Eilam of Veterinary

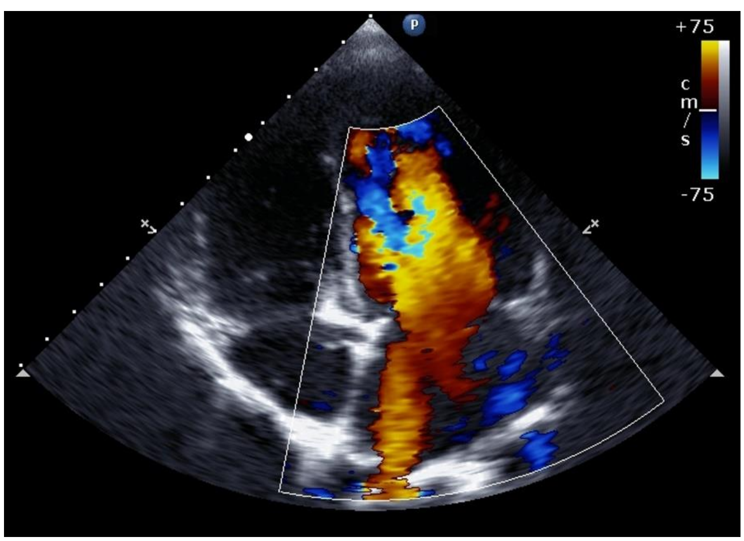
Resources Department, Drs. Alexander Brandis, Sergey Malitsky and Maxim Itkin of Life Sciences Core Facilities Department, Shelly Kalaora, Dr. Ronen Levy and Prof. Yardena Samuels of the Molecular Cell Biology Department, and Dr. Noam Stern Ginossar of the Molecular Genetics Department – all of the Weizmann Institute of Science; Dr. Joo Sang Lee, Hiren Karathia, Noam Auslander and Prof. Sridhar Hannenhalli of the University of Maryland; Daniel Helbling and Dr. David Dimmock of Medical College Wisconsin; Dr. Qin Sun and Dr. Sandesh CS Nagamani of the Baylor College of Medicine; Eilon Barnea and Prof. Arie Admon of the Technion – Israel College of Technology; Miguel Unda and Prof. Arkaitz Carracedo of Basurto University Hospital in Bilbao, Spain; Dr. David M Wilson III of the National Institute on Aging; and Dr. Ronit Elhasid of Tel Aviv Sourasky Medical Center.

Dr. Ayelet Erez's research is supported by the Adelis Foundation; the Rising Tide Foundation; the Comisaroff Family Trust; the Irving B. Harris Fund for New Directions in Brain Research; and the European Research Council. Dr. Erez is the incumbent of the Leah Omenn Career Development Chair.

An Algorithm that Rivals Experts Could Save Lives

A joint venture of the Weizmann Institute of Science and New York University recently won first place in a competition for innovation in echocardiography

Ultrasound equipment has shrunk in both size and price in recent years – so much so that it is standard in hospitals and clinics all over the world. But today's ultrasound still requires a highly-trained expert to acquire the image and interpret the results, and this has prevented its use in certain settings, for example, in urgent care. In a joint venture they call On-Sight, computer scientists at the Weizmann Institute of Science and a cardiologist at the NYU School of Medicine have teamed up to develop an automated system that guides the operator in acquiring the images and then accurately interprets the results for physicians. This venture was recently awarded first place in the third Echovation Challenge of the American Society of Echocardiography.



Electrocardiogram

An echocardiogram is a type of ultrasound that measures the ejection fraction of the heart – that is, the fraction of the blood in the left heart chamber that is ejected to the rest of the body during a heartbeat.

This is considered the most reliable measure of heart function, and if it could be used for immediate diagnosis, this test could save lives.

The 2018 prize was announced at the Society's convention in Nashville. On-Sight was chosen over 30 other entries, as its real time results can help doctors − even non-specialists or medical residents − to make a quick, reliable diagnosis.

To test the system, the On-Sight algorithm vied against four echocardiography experts, its analyses of electrocardiograms from 114 people compared with theirs. The results were stunning: The algorithm was as close as that of the physicians to the external ejection fractions of those hearts.

Experienced ultrasound technicians undergo hours of training, years of practice and ongoing refresher courses. How does one teach a computer to see what these trained experts see? The On-Sight algorithms employ a so-called core neural network, which is based on artificial intelligence and geometric machine learning. This type of system combines the network-based way in which our own brains take in information and make connections with the ability of a computer to rapidly absorb huge amounts of information and to focus on a particular task. Prof. Yaron Lipman of the Computer Science and Applied Mathematics Department of the Weizmann Institute of Science is an expert in the new field of geometric machine learning, which adds layers of complexity to machine neural networks. In this way the "intuitive" diagnoses of multiple experts are translated to the more definitive results of medical tests.

The On-Sight team also includes Achi Ludomirsky, MD, a pediatric cardiology expert at NYU School of Medicine, Itay Kezurer, cofounder and future CTO, and Dr. Yoram Eshel, the company's CEO.

The group chose to focus on cardiologic ultrasound because a timely diagnosis has great potential to save lives in this field. In addition to emergency and urgent care settings, they hope that the technology will eventually be used in nursing homes, sports clinics, ambulances and developing countries.

Prof. Yaron Lipman's research is supported by the European Research Council.

Freezing Fly Eggs for the Future

WISe, the entrepreneurship club for Weizmann Institute of Science students, helped three alumni found a new company that could advance the edible insect market

Flies are packed with protein and nutritious fat; and they grow quickly fed on eat organic waste. One fly in particular, the black soldier fly (*Hermitia illucens*), could potentially provide an alternative, sustainable source of protein in animal feed, and companies around the world are looking into the possibility. A new company founded by three recent Weizmann Institute of Science graduates means to advance the edible insect industry by freezing the eggs of these flies so that growers can better plan and control their yields.

The interest in edible insects has grown in recent years as it has become clear that the present use of 80% of the world's agricultural land to feed animals is unsustainable. Black soldier flies are considered excellent candidates for alternate protein sources because they don't bite or transmit disease, and their larva grow quickly to thousands of times their original size, all on such organic waste as citrus peels or rotting meat. Once grown, they can be ground into flour to make a nutritious additive to animal feed.

The three fresh Weizmann Institute of Science graduates – Drs. Yuval Gilad, Idan Alyagor and Yoav Politi – named their company FREEZEM. As the name suggests, they are developing a way to cryogenically freeze the fly eggs so they remain viable. The technology for freezing fly eggs, they say, is different from that used to freeze human ova or bacteria, and they are the first to offer this development.

The idea of freezing eggs is to separate the fly's life cycle into two: On the one, the reproductive, egg-laying stage and, on the other, growing larvae. This would enable the growers to focus on the correct amounts, conditions and timing to produce the highest yields of insects. "Just as modern farmers buy seed, edible insect growers will buy frozen eggs, thaw them and grow the larvae," says Gilad. The global edible insect market is already estimated to stand at 100 million dollars, but the trade in animal feed is worth around 400 billion. That means that the potential market for such sustainable alternative protein sources as insect flour is huge. The three founders of FREEZEM are hoping that their technology will be the push that is needed to make growing flies efficient, cost-effective and competitive in this market.

The company was conceived in WISe, the entrepreneurship club for Weizmann Institute of Science students. Gilad and Politi have been friends since kindergarten; they met Alyagor through the club. All three had wanted to move from the academic world to industry, and WISe, through meetings with entrepreneurs and industrialists, gave them essential tools for developing a business model and founding their company. They recently signed an agreement with Yeda, the technology transfer arm of the Weizmann Institute, and Yeda has invested in FREEZEM, as well.

For more information:

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