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Science Tips

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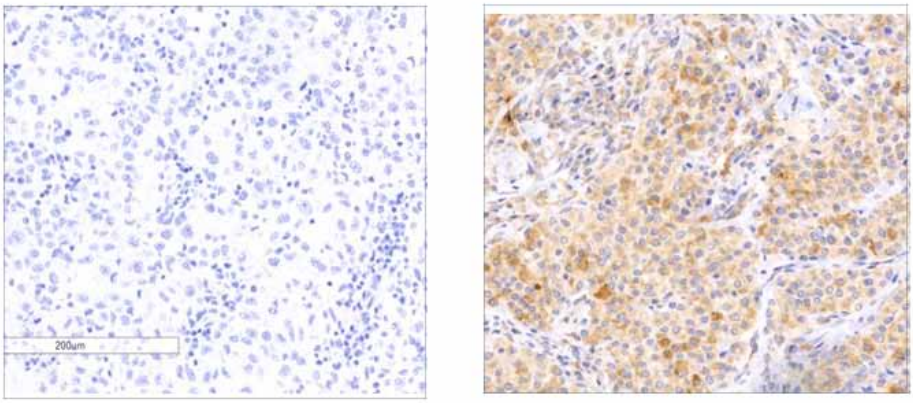
A Newly-Discovered Tumor Suppressor Gene Affects Melanoma Survival

Restoring the function of this gene in melanoma cells caused them to stop growing and die

Of the hundreds of genes that can be mutated in a single case of melanoma, only a handful may be true "drivers" of cancer. In research that recently appeared in *Nature Genetics*, a Weizmann Institute of Science team has now revealed one of the drivers of a particularly deadly subset of melanomas – one that is still seeing a rise in new cases. This gene is a newly identified member of a group of genes called tumor suppressor genes. It is mutated in some 5.4% of melanomas. Furthermore, its expression was found to be lost in over 30% of human melanomas; and this loss, according to the finding, was associated with reduced patient survival. This discovery might open new doors to understanding how this cancer grows and spreads, and it may lead in the future to new directions in treating this disease.

Prof. Yardena Samuels and her team in the Institute's Molecular Cell Biology Department were specifically searching for tumor suppressor genes in their database, which consists of more than 500 melanoma genomes and exomes – protein-building sequences – making it the largest melanoma dataset to date. As their name suggests, tumor suppressor genes normally inhibit cell growth, including that of cancer cells. However, when mutated, they act like defective brakes on cellular proliferation. Thus studying these genes is crucial in cancer biology. "The identification of targetable alterations in melanoma is an urgent need. An in-depth understanding of the functional effects of mutations in these genes is the first step toward revealing the underlying mechanism of melanoma growth," says Dr. Nouar Qutob, a postdoctoral fellow in Samuels' lab who participated in this research.



Metastatic melanoma tumors. Left exhibits low or absent expression of RASA2 and reduced survival, typical of about 35% of patients. The sample on the right exhibits high RASA2 expression and increased survival

When mutated, they act like defective brakes on cellular proliferation

Indeed, the melanoma genome sequences contained mutations in known tumor suppressor genes, but there was also a new gene that stood out in the team's search, named RASA2. The researchers' next step was to conduct a series of functional experiments to understand exactly what this gene does. They cloned both the normal protein and the most recurrent mutated versions to see their effects on melanoma cells. They found that RASA2 regulates a key protein in the cell, called RAS. RAS has been identified as a major oncogene that contributes to the unchecked growth of cells. When they restored the production of the protein in melanoma cells that harbored RASA2 mutations, these cells stopped growing and eventually died.

Patients with dysfunctional RAS pathways tend to have a worse prognosis than those with other types of melanoma, and, until now, scientists have not managed to create drugs that can target this pathway. "As the RAS pathway is highly dysregulated in cancer, the discovery of an alternative mechanism for its activation is likely to stimulate an avalanche of

further research in this field, and is highly likely to have direct clinical relevance. We are now going to focus on RASA2, to find out what proteins it communicates with in healthy cells and melanoma, as well as in the cells' response to targeted therapy," says Samuels. "Most targeted cancer therapies nowadays work by inhibiting the products of oncogenes that are overactive in melanoma cells. However, loss or mutations in tumor suppressor genes like RASA2 also contribute to melanoma development; therefore, discovering and studying RASA2 targets and partners will be our next aim," says Rand Arafeh, a PhD student in Samuels' lab and lead author of the paper.

Prof. Yardena Samuels' research is supported by the Ekard Institute for Diagnosis, which she heads; the Henry Chanoch Krenter Institute for Biomedical Imaging and Genomics; the Laboratory in the name of M.E.H Fund established by Margot and Ernst Hamburger; the Louis and Fannie Tolz Collaborative Research Project; the Dukler Fund for Cancer Research; the European Research Council; the De Benedetti Foundation-Cherasco 1547; the Peter and Patricia Gruber Awards; the Comisaroff Family Trust; the Rising Tide Foundation; Sharon Zuckerman, Canada; Charles Rothschild, Brazil; the estate of Alice Schwarz-Gardos; the estate of John Hunter; and the estate of Adrian Finer. Prof. Samuels is the incumbent of the Knell Family Professorial Chair.

http://www.nature.com/ng/index.html

Immune Cells that Fight Obesity

Mice lacking certain immune cells become overweight, even on a normal diet

We tend to think of the immune system as guarding us against bacteria, viruses, and other foreign invaders, but this system has other surprising roles. Weizmann Institute researchers have now identified a small subtype of immune cells that appears to prevent metabolic syndrome: obesity, high blood pressure, and high levels of blood sugar and cholesterol.

Past studies have shown that the immune system plays a role in obesity, but those studies were performed on mice deliberately fed a high-fat diet. The new Weizmann study, published recently in *Immunity*, was performed on mice fed a regular diet. It showed that immunological mechanisms can play a role in obesity and the other components of metabolic syndrome without connection to dietary fat.

The study originally focused on dendritic cells, cells that serve as the immune system's sentinels, alerting other immune mechanisms to various dangers. The emphasis was on a rare subtype of dendritic cells possessing a killing protein called perforin that enables them to eliminate other cells on demand. To reveal the function of these cells in the body, researchers headed by Prof. Yair Reisner of the Immunology Department created mice that lacked perforin-rich dendritic cells. To their surprise, the scientists discovered that these mice became overweight and then developed symptoms of metabolic syndrome.

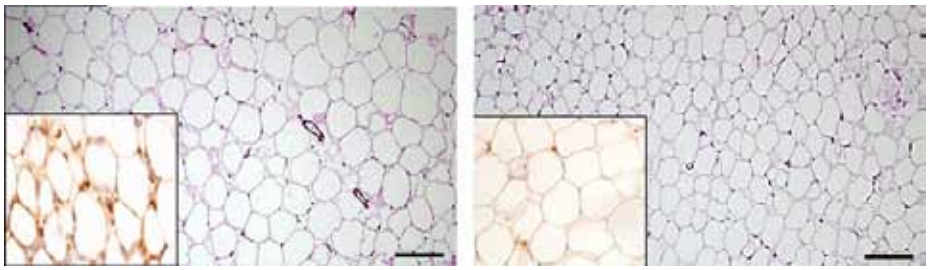
Investigating these mice further, the researchers found that their fat tissue had abnormally high levels of inflammation-causing immune T cells. When these cells were removed from the fat tissue of the mice lacking perforin-rich dendritic cells, the mice did not grow obese. These findings suggest that perforin-rich dendritic cells regulate the levels of certain T cells, and by keeping these T cells in check, they apparently prevent metabolic syndrome.

To their surprise, the scientists discovered that these mice became overweight and then developed symptoms of metabolic syndrome

In addition to providing new insights into metabolic syndrome, the study may also shed new light on autoimmunity: the mice lacking perforin-rich dendritic cells were more prone than usual to develop an autoimmune disease equivalent to multiple sclerosis in humans. It now remains to be investigated whether patients with autoimmune disease lack these regulatory cells.

The study was performed by members of Reisner's team, in collaboration with Institute colleagues, all of whom are from the Immunology Department: Dr. Yael Zlotnikov-Klionsky, Bar Nathansohn-Levi, Dr. Elias Shezen, Dr. Chava Rosen, Dr. Sivan Kagan, Dr. Liat Bar-On, Prof. Steffen Jung, Dr. Eric Shifrut, Dr. Shlomit Reich-Zeliger, Dr. Nir Friedman, Dr. Rina Aharoni, Prof. Ruth Arnon, Oren Yifa and Dr. Anna Aronovich.

Prof. Yair Reisner's research is supported by the Leona M. and Harry B. Helmsley Charitable Trust; the Steven and Beverly Rubenstein Charitable Foundation; and Roberto and Renata Ruhman, Brazil. Prof. Reisner is the incumbent of the Henry H. Drake Professorial Chair of Immunology.



Fat tissue cells are enlarged and more loosely packed in mice lacking perforin-rich dendritic cells (left) compared with the fat tissue of regular mice (right). Inset: crown-like structures within the fat tissue (left, dark brown) are associated with increased inflammation

http://www.cell.com/immunity/abstract/S1074-7613%2815%2900347-7

Plants Keep One Foot on the Brakes

Why would plants use a seemingly inefficient method for controlling starch production?

Pressing on the gas and the brakes at the same time hardly sounds like a good driving technique, but Weizmann Institute scientists have discovered that plants drive some of their key processes precisely in such a manner.

A research team headed by Prof. Avihai Danon of the Plant and Environmental Sciences Department – postdoctoral fellow Dr. Erez Eliyahu and then graduate students Ido Rog and Inbal Dangoor – studied the mechanisms controlling the plant production of starch, the most common carbohydrate in the human diet. The plant starts making starch as soon as the morning light turns on photosynthesis and stops when photosynthesis subsides at night.

It's as if the plant drives its starch production by pressing on the gas pedal and the brakes simultaneously

About half a century ago, scientists discovered the "on" switch for starch production: a launch enzyme that is activated, via a series of regulatory proteins, by the flow of electrons generated in photosynthesis. Now in the new study, reported in the *Proceedings of the National Academy of Sciences*, USA, Weizmann Institute scientists have discovered the "off" switch for starch production. Working with a mustard-like plant called *Arabidopsis*, they figured out the chain of biochemical events leading to its shutdown at night. The decrease in light causes a small signaling protein called ACTH4 to lose electrons and become oxidized, which, in turn, quickly prompts it to transmit the "take a break" message to the starch production enzyme.

The scientists further realized that this mechanism remains active at a low level throughout the day. It's as if the plant drives its starch production by pressing on the gas pedal and the brakes simultaneously: turning the production on while at the same time keeping it in check. When the scientists genetically engineered the plants to eliminate the "brakes," starch production shot up by nearly 20 percent. This suggests that in general, production efficiency stands at only about 80 percent because this brake pedal is on all the time. In the future, this research may make it possible to increase starch production in agricultural crops.

Why do plants naturally produce starch in such an inefficient manner?

Since light intensity, and with it the rate of photosynthesis, often fluctuates rapidly throughout the day, the plant needs to adjust its metabolism on an ongoing basis. Starch synthesis in particular needs to be closely attuned to photosynthesis so that the compounds created in photosynthetic reactions are promptly taken up – otherwise reactive oxygen molecules called free radicals, generated as a byproduct of photosynthesis, can build up in excess and harm the plant.

Pressing the "gas" and the "brake pedals" simultaneously enables plants to control their starch production rapidly and effectively via adjusting the relative strengths of the two. Keeping the brake pedal slightly pressed most of the time leaves room for a potential increase should sunlight suddenly become extremely intense. Keeping one foot on the brakes is therefore part of the sophisticated set of control mechanisms that has helped plants survive over hundreds of millions of years.

Prof. Avihai Danon's research is supported by the Raymond Burton Plant Genome Research Fund; the Lerner Family Plant Science Research Fund; the Leona M. and Harry B. Helmsley Charitable Trust; the Jacob and Charlotte Lehrman Foundation; Mr. Jack N. Halpern, New York, NY; and Adolfo Eric Labi, Italy. Prof. Danon is the incumbent of the Henry and Bertha Benson Professorial Chair.

Arabidopsis. Like other plants, it has evolved to cope with abrupt changes in light intensity

http://www.pnas.org/content/112/41/12876.full?sid=d09d51cd-0808-49ad-b08f-25d9b80ac7a3