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Science Tips

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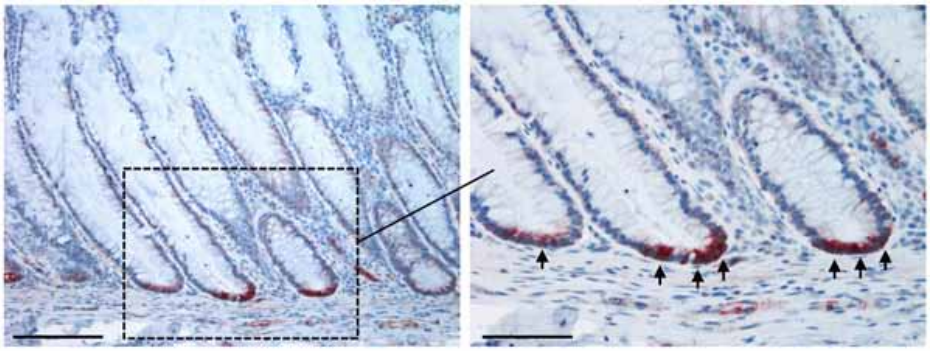
Colon Cancer: Taking a Step Back to Move Forward

Recent Weizmann Institute studies are revealing a complex picture of cancer progression in which certain genes that drive tumor growth in the earlier stages get suppressed in later stages – taking a step back to move forward. Current research in the lab of Prof. Avri Ben-Ze'ev of the Molecular Cell Biology Department suggests that the tumor cells at the invasive front of later-stage human colorectal cancer may take an even bigger step back: Some of their gene expression patterns are shared with those of healthy intestinal stem cells.



Normal human colonic crypts. SMOC-2 expression (red) in the colonic stem cells demonstrates that these cells are localized in the bottoms of the crypts. Bars represent 100 micrometers (left) and 50 micrometers (right)

Colorectal cancer is most deadly when the cancer has metastasized – spread to other organs in the body, mainly to the liver. Ben-Ze'ev and his team had previously discovered that a mutation found in 80% of all colorectal cancers leads to enhanced expression of another gene, called L1, especially in the cells at the leading edge of metastatic growth. L1 is known to play a role in cell-to-cell adhesion; in the present study, further investigation into L1 expression led the group to yet another gene, called SMOC-2.

The researchers investigated the role of this gene in mouse models of colorectal cancer metastasis to the liver, finding that L1 produced heightened SMOC-2 levels during this stage. When the researchers increased the levels of SMOC-2 in human colorectal cancer cells, their metastasis to the liver was fast and aggressive. Conversely, blocking the gene in colon cancer cells inhibited metastasis, conclusively indicating that the activation of SMOC-2 by L1 plays a crucial role in the spread of this cancer.

Similarly elevated SMOC-2 levels had been seen by another group – in mouse intestinal stem cells, which provide replacements for the cells in the intestinal walls. Ben-Ze'ev's group found that SMOC-2 is normally expressed in the colon exclusively in the stem cells' protected niches at the bottom of the tube-like "colon crypts." In human colorectal cancer, in contrast, the gene was expressed in the more invasive regions of the tumor.

What does this gene do? SMOC-2 encodes a molecule that is secreted by the cells and then makes it way to the outer part of the cell membrane, where it facilitates movement. This molecule is thought to help differentiating stem cells disengage from their neighbors and make their ascent up the colon crypt walls. Similarly, metastatic human colon cancers seem to activate this gene to enable them to "leave home" and make their way out.

This research, says Ben-Ze'ev, provides support for the idea that as cancer develops it also reverts – that is, some of its cells adopt a less mature, more stem-like, state that assists metastasis. Additional investigations into the interactions between SMOC-2 and other genes suggested that the human cancer cells were, indeed, taking on some qualities of stem cells.

Ben-Ze'ev hopes that further research will point to ways of interfering with the activities of genes like SMOC-2, thus preventing this cancer from metastasizing. In addition, he says, the expression patterns of SMOC-2 could make it an ideal marker for the early detection of human metastatic colorectal cancer.

Prof. Avri Ben-Ze'ev is the incumbent of the Samuel Lunenfeld-Reuben Kunin Chair of Genetics.

http://www.nature.com/onc/journal/vaop/ncurrent/full/onc2015127a.html

Seeing a Supernova in a New Light

Type Ia supernovae are the "standard candles" astrophysicists use to chart distance in the Universe. But are these dazzling exploding stars truly all the same? To answer this, scientists must first understand what causes stars to explode and become supernovae. Recently, a unique collaborative project between the California Institute of Technology (Caltech) and the Weizmann Institute of Science provided a rare glimpse of the process. Their findings were published in *Nature*.

The project, the Palomar Transient Factory, is a robotic telescope system based in Southern California that scans the night sky for changes. In May, halfway around the world at the Weizmann Institute, Dr. Ilan Sagiv realized that one of the bright new lights the Palomar telescope had pinpointed was, indeed, a supernova – just four days into the explosion – and he sounded the alert sending the Swift Space Telescope on NASA's Swift Satellite to observe the blast. But the Swift Telescope also observed in an unusual way – in the invisible, ultraviolet range.

This spike fits a model in which a dwarf star has a giant companion

"Ultraviolet is crucial," says the Weizmann Institute's Prof. Avishay Gal-Yam of the Particle Physics and Astrophysics Department, "because initially, supernova blasts are so energetic that the most important information can only be gathered in short wavelengths. And it can only be seen from a space telescope, because the ultraviolet wavelengths are filtered out in the Earth's atmosphere."

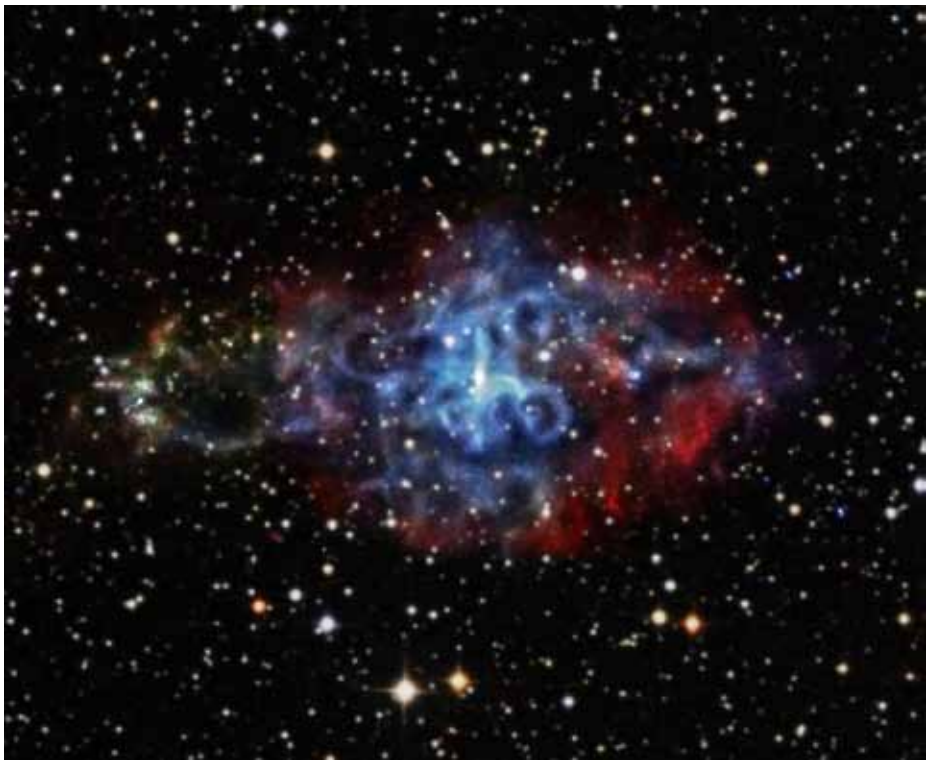
The researchers collected observations ranging from the energetic X-ray and UV all the way to the radio wavelengths, the latter effort led by the Institute's Dr. Assaf Horesh. Caltech graduate student Yi Cao, who was the lead author on the paper, and his advisor Prof. S. Kulkarni, compared the figures from the observations to various models to see which fit. Astrophysicists mostly agree that the exploding stars that become type Ia supernova are extremely dense, old stars called white dwarves. But a number of models have been proposed to explain what makes them suddenly blow up.

Ultraviolet observation enabled the researchers to see something they had never seen before: a unique, brief spike in the high-energy radiation very early on. This spike, says Gal-Yam, fits a model in which a dwarf star has a giant companion. "The white dwarf is the mass of the Sun packed into a sphere the size of the Earth, while its companion is around 50-100 times bigger around than the Sun." Material flows from the diffuse star to the dense one until, at some point the pressure from the added mass causes the smaller star to detonate. The radiation spike is caused by the initial material thrown off in the blast slamming into the companion.

Gal-Yam says that the group's findings show, among other things, the importance of ultraviolet-range observations. He is hopeful that the ULTRASAT mini-satellite planned by the Weizmann Institute's Prof. Eli Waxman, together with other researchers, the Israeli Space Agency and NASA, which will observe in the ultraviolet range, will help researchers discover whether this explosive process is common to type Ia supernovae.

Prof. Avishay Gal-Yam's research is supported by the Helen and Martin Kimmel Award for Innovative Investigation; the Helen Kimmel Center for Planetary Science; the Nella and Leon Benoziyo Center for Astrophysics; and the Benoziyo Endowment Fund for the Advancement of Science.

Prof. Eli Waxman's research is supported by the Nella and Leon Benoziyo Center for Astrophysics, which he heads. Prof. Waxman is the incumbent of the Max Planck Professorial Chair of Quantum Physics.



Supernova 3C58, first observed in the year 1181 AD by Chinese and Japanese astronomers, imaged by the Chandra telescope in X-ray emissions. NASA/CXC/SAO

http://www.nature.com/nature/journal/v521/n7552/full/nature14440.html

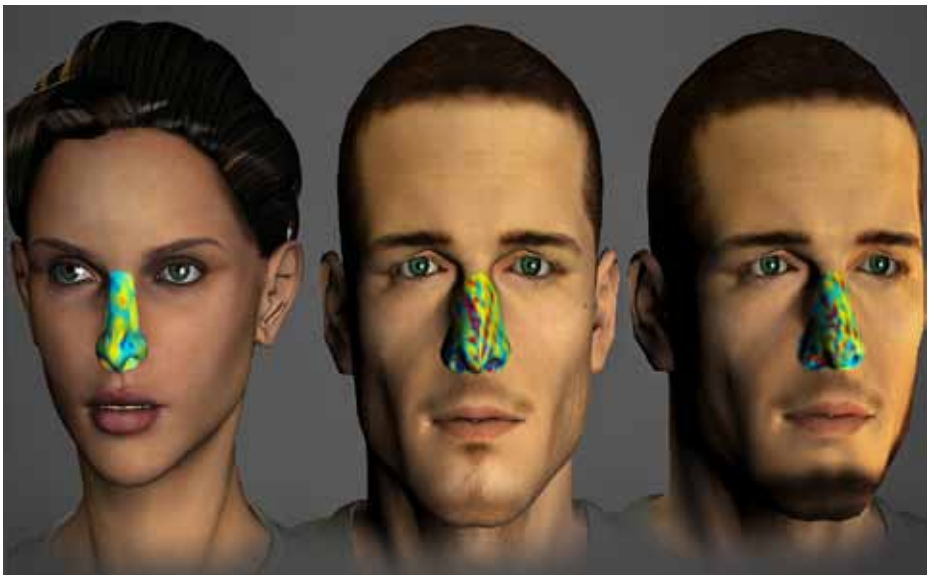
Fingerprinting Our Sense of Smell

Each of us has, in our nose, about six million smell receptors of around four hundred different types. The distribution of these receptors varies from person to person – so much so that each person's sense of smell may be unique. In research recently published in the *Proceedings of the National Academy of Sciences* (PNAS), Weizmann Institute scientists report on a method of precisely characterizing an individual's sense of smell, which they call an "olfactory fingerprint."

The implications of this study reach beyond the sense of smell alone, and range from olfactory fingerprint-based early diagnosis of degenerative brain disorders to a non-invasive test for matching donor organs.

The method is based on how similar or different two odors are from one another. In the first stage of the experiment, volunteers were asked to rate 28 different smells according to 54 different descriptive words, for example, "lemony," or "masculine." The experiment, led by Dr. Lavi Secundo, together with Dr. Kobi Snitz and Kineret Weissler, all members of the lab of Prof. Noam Sobel of the Weizmann Institute's Neurobiology Department, developed a complex, multidimensional mathematical formula for determining, based on the subjects' ratings, how similar any two odors are to one another in the human sense of smell. The strength of this formula, according to Secundo, is that it does not require the subjects to agree on the use and applicability of any given verbal descriptor. Thus, the fingerprint is odor dependent but descriptor and language independent.

The 28 odors make for 378 different pairs, each with a different level of similarity. This provides us with a 378-dimensional fingerprint. Using this highly sensitive tool, the scientists found that each person indeed has an individual unique pattern – an olfactory fingerprint.



The olfactory fingerprint of the person in the middle remains consistent, even after 30 days (right), but is very different from that of another person (left)

Could this finding extend to millions of people? The researchers say their computations show that 28 odors alone could be used to "fingerprint" some two million people, and just 34 odors would be enough to identify any of the seven billion individuals on the planet.

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The next stage of the research suggested that our olfactory fingerprint may tie in with another system of ours in which we all differ – the immune system. They found, for example, that an immune antigen called HLA, today used to assess matches for organ donation, is correlated with certain olfactory fingerprints. This part of the study was conducted together with Drs. Ron Loewenthal, and Nancy Agmon-Levin, and Prof. Yehuda Shoenfeld, all of Sheba Medical Center.

The researchers think that olfactory fingerprinting, in addition to helping identify individuals, could be developed into methods for the early detection of such diseases as Parkinson's and Alzheimer's, and it could lead to non-invasive methods of initial screening as to whether bone marrow or organs from live donors are a good match.

Prof. Noam Sobel's research is supported by the Norman and Helen Asher Center for Brain Imaging, which he heads; the Nella and Leon Benoziyo Center for Neurosciences, which he heads; the Carl and Micaela Einhorn-Dominic Institute for Brain Research, which he heads; the Nadia Jaglom Laboratory for the Research in the Neurobiology of Olfaction; the Adelis Foundation; the James S. McDonnell Foundation 21st Century Science Scholar in Understanding Human Cognition Program; Mr. & Mrs. H. Thomas Beck, Canada; the Minerva Foundation; the European Research Council; Nathan and Dora Oks, France; Mike and Valeria Rosenbloom through the Mike Rosenbloom Foundation; and the Estate of David Levidow.

http://www.pnas.org/content/early/2015/06/17/1424826112.short