מכון ויצמן למדע
WEIZMANN INSTITUTE OF SCIENCE

Science Tips

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Wake up and Smell the Sweat

Some people are oblivious to the odor in the locker room after a game, while others wrinkle their noses at the slightest whiff of sweat. Research by Prof. Doron Lancet and research student Idan Menashe of the Molecular Genetics Department, which appeared recently in *PLoS Biology*, has now shown that this difference is at least partly genetic.

Our sense of smell often takes a back seat to our other senses, but humans can perceive up to 10,000 different odors. Like mice, which boast a highly-developed sense of smell, we have about 1000 different genes for the smell-detecting receptors in our olfactory "retinas." In humans, however, over half of these genes have, in the last few million years, become defunct – some in all people, while others in just parts of the population.

Lancet and his team had their experimental volunteers sniff varying concentrations of compounds that smelled like banana, eucalyptus, spearmint or sweat, and noted the sensitivity with which the subject was able to detect the odor. They then compared the results with genetic patterns of receptor gene loss and found that one gene (OR11H7P) appeared to be associated with the capacity for smelling sweat. When participants had two genes with disrupting mutations, they were likely to be impervious to the offending odor, while those that were hypersensitive to the smell had at least one intact gene.

The scientists noted, however, that while having at least one intact OR11H7P gene might determine whether you can tell by the smell that your loved one has just come from the gym, this is not the entire story. Women were generally slightly more sensitive to many smells than men, and some individuals of both sexes were better or worse in across-the-board acuity to all odorants. Finally (as is always the case), not all was in the genes – environmental factors were seen to play a role as well. ❙

Prof. Doron Lancet's research is supported by the Nella and Leon Benoziyo Center for Neurological Diseases; the Crown Human Genome Center; and the Laub Fund for Oncogene Research. Prof. Lancet is the incumbent of the Ralph and Lois Silver Professorial Chair in Human Genomics.

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Repeating Genes

Huntington's disease is a genetic time bomb: Programmed in the genes, it appears at a predictable age in adulthood, causing a progressive decline in mental and neurological function and finally death. There is, to date, no cure. Huntington's, and a number of diseases like it, collectively known as trinucleotide repeat diseases, are caused by an unusual genetic mutation: A three-letter piece of gene code is repeated over and over in one gene. Scientists at the Weizmann Institute have now proposed a mechanism that provides an explanation for the remarkable precision of the time bomb in these diseases. This explanation may, in the future, point researchers in the direction of a possible prevention or cure.

The number of repeats in Huntington's patients ranges from 40 to over 70. Scientists have noted that, like clockwork, one can predict by how many times the sequence repeats in a patient's gene both the age at which the disease will appear and how quickly the disease will progress. The basic assumption has been that the protein fragment containing the amino acid (glutamine) encoded in the repeating triplet slowly builds up in the cells until eventually reaching toxic levels. This theory, unfortunately, fails to explain some of the clinical data. For instance, it doesn't explain why patients with two copies of the Huntington's gene don't exhibit symptoms earlier than those with a single copy. Plus, glutamine is produced in only some trinucleotide diseases, whereas the correlation between sequence length and onset age follows the same general curve in all of them, implying a common mechanism not tied to glutamine.

Research student Shai Kaplan in Prof. Ehud Shapiro's lab in the Biological Chemistry, and Computer Sciences and Applied Mathematics Departments, realized the answer

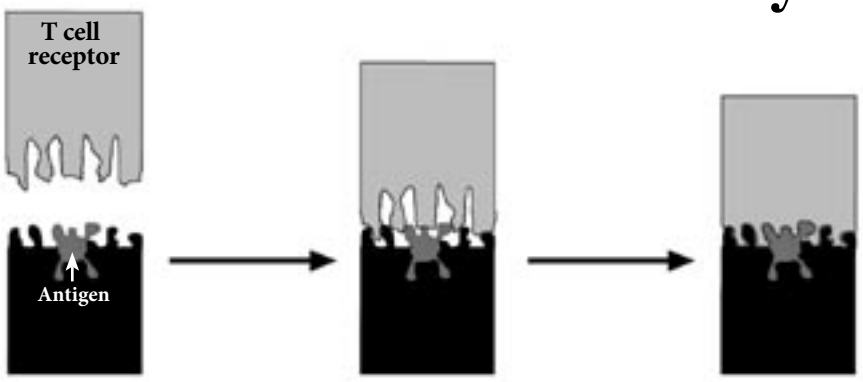
might lie in somatic mutations – changes in the number of DNA repeats that build up in our cells throughout our lives. The longer the sequence, the greater the chance of additional mutation, and the scientists realized that the genes carrying the disease code might be accumulating more and more DNA repeats over time, until some critical threshold is crossed.

Based on the literature on some 20 known trinucleotide repeat diseases and their knowledge of the mechanisms governing somatic mutation, Shapiro, Kaplan (who is also in the Molecular Cell Biology Department) and Dr. Shalev Itzkovitz created a computer simulation that could take a given number of genetic repeats and show both the age of onset and the way in which the disease progresses. Their findings appeared in *PLoS Computational Biology*.

The new disease model appears to fit all of the facts and to provide a good explanation for the onset and progression of all of the known trinucleotide repeat diseases. Experimentation in research labs could test this model, say the scientists and, as it predicts that all these diseases operate by somatic expansion of a trinucleotide repeat, it also suggests that a cure for all might be found in a drug or treatment that slows down the expansion process. ❙

Prof. Ehud Shapiro's research is supported by the Clore Center for Biological Physics; the Arie and Ida Crown Memorial Charitable Fund; the Cymerman - Jakubskind Prize; the Fusfeld Research Fund; the Henry Gutwirth Fund for Research; Ms. Sally Leafman Appelbaum, Scottsdale, AZ; the Louis Chor Memorial Trust Fund; and the estate of Fannie Sherr, New York, NY. Prof. Shapiro is the incumbent of the Harry Weinrebe Chair of Computer Science and Biology.

Bound to Identify Intruders



In the first, fast stage of binding, superficial contact is produced between the T cell receptor binding site (gray) and the antigen protein on the target cell (black). In the second, slower stage, a conformational transition takes place in the receptor's structure, leading to the final stable configuration.

The first lines of defense in our immune systems are specialized mobile units that check the identity of cells to determine whether they are "self" or "foreign." A team of scientists, led by Prof. Israel Pecht of the Weizmann Institute's Immunology Department, has now revealed in fine detail how the body's "reconnaissance unit" continuously screens and inspects identity. These new findings may lead to deeper insights into the workings of the immune system, its function in health and malfunction in disease, as well as yielding new directions in pharmaceutical and medical research.

White blood cells called T cells employ specialized receptors called TCRs (T cell receptors) for cell identification. TCRs bind to molecules present on all our body's cells that act as "self-I.D. cards." Small fragments of bodily components bound to grooves in these molecules provide additional confirmation that the cell is ours and intruder-free. T cell receptors, when they examine the these complexes (antigens), are able to spot foreign bits, even when one amino acid in the antigen is out of order, and can pick just one infected cell out of thousands of healthy ones, even when they harbor a previously unknown virus.

How does this interaction take place? Pecht, together with colleagues in Germany and France, has now provided the first step-by-step understanding of the process. Using a method that resolves these biological events at millisecond (a thousandth of a second) intervals, they were able to show how TCR binding progresses through time. Their findings recently appeared in the *Proceedings of the National Academy of Sciences (PNAS)*, USA.

The team found that binding of the TCR to the antigen takes place in two separate stages, confirming the widely-held theory that the process is an "induced fit": The original physical contact between the two molecules initiates the second step, in which conformational changes occur in the receptor as it molds itself to fit the antigen shape.

This research, says Pecht, may go a long way toward explaining a seeming paradox of long standing: How T cells can be highly specific – able to precisely identify a particular protein structure – and yet able to bind to a very wide variety of protein molecules. Additional studies based on this research may clarify the process further – shedding light on the causes of autoimmune diseases and infections such as HIV that evade the immune system, as well as advancing the search for new drugs and treatments for a variety of diseases.

Also participating in this research were Dmitry Gakamsky of the Institute's Immunology Department; Erwin Lewitzki and Ernst Grell of the Max Planck Institute of Biophysics, Germany; Xavier Saulquin, Bernard Malissen and Marc Bonneville of the National Institute of Health and Medical Research, France; and Felix Montero-Julian of Beckman Coulter, France. ❙