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Publications and Media Relations Department, Rehovot, Israel 76100 Tel: 972-8-934-3852 / 56 Fax: 972-8-934-4132
http://wis-wander.weizmann.ac.il news@weizmann.ac.il January 2007

Calculated Risk

Weizmann Institute scientists discover a genetic risk factor for smoking-linked head and neck cancer

A simple blood test may be able to identify those most at risk for developing head and neck cancer as a result of smoking. This was the finding of a recent study by Prof. Zvi Livneh, Head of the Weizmann Institute's Biological Chemistry Department, Dr. Tamar Paz-Elizur of the same department, and their research team that worked in collaboration with Dr. Rami Ben-Yosef of Tel Aviv-Sourasky Medical Center, Prof. Laurence Freedman of Sheba Medical Center and Prof. Edna Schechtman of Ben-Gurion University of the Negev.

Livneh's research deals with repair mechanisms for DNA, the material of genes. Cells maintain sophisticated repair systems to prevent the accumulation of mutations that might lead to cancer. In these systems, molecular detectors scan the DNA for injury. A sort of local operation is then performed to cut out and dispose of the damaged segment and replace it with a new one.

In their study, which appeared in *Cancer Research*, the scientists asked whether a reduced individual ability (non-inherited) to repair DNA damage increases chances of getting head and neck cancer. Smoking damages DNA and is known to be a major cause of this disease, which can affect the throat, mouth and larynx. The researchers focused on a DNA repair enzyme called OGG1, for which they had previously developed a blood test to measure activity levels. By comparing OGG activity in healthy people with those in head and neck cancer patients, the research team found that the test was able to single out those with a heightened risk of this type of cancer: Weak levels were correlated with greater risk. According to Prof. Livneh, a smoker with low OGG activity is 70 times more likely to develop head and neck cancer than a non-smoker with normal OGG levels.

These findings join a previous study by the group in which they found that low OGG activity is an indicator of elevated risk for lung cancer, a disease also caused by smoking. Together, these studies show that a combination of low OGG activity and smoking can skyrocket a person's chances of becoming ill with a smoking-related cancer. Also participating in the study were Dalia Elinger of the Biological Chemistry Department, Dr. Akiva Vexler of Tel Aviv-Sourasky Medical Center, Profs. Adi Shani and Alain Berrebi of Kaplan Medical Center, and Dr. Meir Krupsky of Sheba Medical Center.

The OGG blood test might be used, in the future, to identify those most at risk for lung and head and neck cancers, hopefully giving added incentive to those with the risk factor to quit smoking. In addition, drugs might be developed to reduce this risk, similar to those prescribed today to reduce the risk of heart disease. ❙

Prof. Zvi Livneh's research is supported by the M.D. Moross Institute for Cancer Research; the Dr. Josef Cohn Minerva Center for Biomembrane Research; the J & R Center for Scientific Research; the Levine Institute of Applied Science; and the Flight Attendant Medical Research Institute. Prof. Livneh is the incumbent of the Maxwell Ellis Professorial Chair in Biomedical Research.

Complex Channels

Weizmann Institute scientists discover how ion channels are organized to effectively control nerve cell communication

The messages passed in a neuronal network can target something like 100 billion nerve cells in the brain alone. These, in turn communicate with millions of other cells and organs in the body. How, then, do whole cascades of events trigger responses that are highly specific, quick and precisely timed? A team at the Weizmann Institute of Science has now shed light on this mysterious mechanism. Their discovery could have important implications for the future development of drugs for epilepsy and other nervous system diseases. These findings were recently published in the

journal *Neuron*.

The secret is in the control over electrical signals generated by cells. These signals depend on ion channels – membrane proteins found in excitable cells, such as nerve cells – that allow them to generate electrical signals, depending on whether the channels are opened or closed. Prof. Eitan Reuveny, together with Ph.D. students Inbal Riven and Shachar Iwanir of the Weizmann Institute's Biological Chemistry Department, studied channels that work on potassium ions and are coupled to a protein called the G protein, which when activated, causes the channel to open. Opening the channel inhibits the conductance of electrical signals, a fact that might be relevant, for example, in the control of seizures.

The G protein itself is activated by another protein, a receptor, which gets its cue to carry out its task from chemical messengers known as neurotransmitters. But neurotransmitters are general messengers – they can inhibit as well as excite, and the receptors can respond to either message. How, the scientists wanted to know, is the G protein targeted so quickly and precisely to activate the channel?

Mutations in ion channels are likely to be involved in epilepsy, chronic pain, neurodegenerative diseases and muscular diseases

Reuveny and his team found that the receptor and G protein are physically bound together in a complex, allowing the process to be finely tuned. When the receptor receives a chemical message from the neurotransmitter, it is already hooked up to the correct G protein. After being activated by the receptor, the G protein changes shape, opening the ion channel. The evidence for this complex structure came from special technique called FRET (Fluorescence Resonance Energy Transfer) that can measure the distance between two molecules. The scientists observed that even without stimulation, there is a lot of energy transfer between the G protein and the potassium channel, suggesting that they are very close together.

Mutations in ion channels are likely to be involved in epilepsy, chronic pain, neurodegenerative diseases and muscular diseases, and ion channels are the target of many drugs. Understanding the basic biological phenomena behind the way proteins organize themselves and orchestrate biological processes may allow scientists to design better or more efficient drugs. ❙

Prof. Eitan Reuveny's research is supported by the Y. Leon Benoziyo Institute for Molecular Medicine; the Clore Center for Biological Physics; and the Dr. Josef Cohn Minerva Center for Biomembrane Research.

Weizmann Institute scientists create:

The First Molecular Keypad Lock

Keypad locks, such as those for preventing auto theft, allow an action to take place only when the right password is entered: a series of numbers punched in a pre-set sequence. Now, a team of scientists at the Weizmann Institute of Science has created a molecule that can function as an ultra-miniaturized version of a keypad locking mechanism. Their work appeared in the *Journal of the American Chemical Society* (JACS).

The molecule, synthesized in the lab of Prof. Abraham Shanzer of the Organic Chemistry Department, is composed of two smaller linked units – fluorescent probes – separated by a molecular chain to which iron can bind. One of these probes can shine bright fluorescent blue and the other fluorescent green, but only if the surrounding conditions are right. These conditions are the keypad inputs: Rather than the electric pulses of an electronic keypad, they consist of iron ions, acids, bases, and ultraviolet light.

Shanzer and his group, which includes Drs. David Margulies, Galina Melman and Clifford Felder, have demonstrated in the past that such molecules can be used as logic gates, such as those that form the basis of computer operations. As opposed to electronic logic gates, in which electrical switches flip ON and OFF, the team's molecules, with various combinations of chemical and light inputs, can switch between colors and light intensities to perform arithmetic calculations.

The challenge in creating a keypad lock was in generating sequences that can be distinguished one from another. Entering the sequence 2+3+4 will yield the same result as 3+4+2 on a calculator, but a keypad lock set to one password (234) won't open for the other (342). The scientists found that by controlling the opening rate of the logic gate within the reaction time frame, they were able to produce different, distinguishable outputs, depending on the input order. By adding light energy, which also influences the molecules' glow, they were able to produce a molecule-size device that lights up only when the correct chemical 'passwords' are introduced. "It's just like a tiny ATM banking machine," says Shanzer.

They were able to produce a molecule-size device that lights up only when the correct chemical 'passwords' are introduced

Although these minuscule keypads are not likely to become a practical alternative to today's anti-theft devices, Shanzer believes this example of a molecular keypad lock – the first of its kind – will lead to new ideas and inventions in other areas such as information security and even medicine. "Faster and more powerful molecular locks could serve as the smallest ID tags, providing the ultimate defense against forgery." In the future, molecular keypads might prove valuable, as well, in designing 'smart' diagnostic equipment to detect the release of biological molecules or changes in conditions that indicate disease. ❙

Prof. Abraham Shanzer's research is supported by the Nella and Leon Benoziyo Center for Neurological Diseases; the J & R Center for Scientific Research; the Helen and Martin Kimmel Center for Molecular Design; the Schmidt Minerva Center for Supramolecular Architectures; and Mr. and Mrs. Mordechai Glikson, Israel.