



מכון ויצמן למדע

WEIZMANN INSTITUTE OF SCIENCE

Science *Tips*

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 May 2009

Stopgap DNA Repair Needs a Second Step

One can have a dream, two can make that dream so real, goes a popular song. Now a Weizmann Institute study has revealed that it takes two to perform an essential form of DNA repair.

Prof. Zvi Livneh of the Weizmann Institute's Biological Chemistry Department has been studying DNA repair for some two decades: "Considering that the DNA of each cell is damaged about 20,000 times a day by radiation, pollutants and harmful chemicals produced within the body, it's obvious that without effective DNA repair, life as we know it could not exist. Most types of damage result in individual mutations – genetic 'spelling mistakes' – that are corrected by precise, error-free repair enzymes. Sometimes, however, damage results in more than a mere spelling mistake; it can cause gaps in the DNA, which prevent the DNA molecule from being copied when the cell divides, much like an ink blot or a hole on a book page interferes with reading. So dangerous are these gaps that the cell resorts to a sloppy but efficient repair technique to avoid them:

It fills in the missing DNA in an inaccurate fashion. Such repair can save the cell from dying, but it comes at a price: this error-prone mechanism, discovered at the Weizmann Institute and elsewhere about a decade ago, is a major source of mutations."

In a recent study he conducted with graduate students Sigal Shachar and Omer Ziv, as well as researchers from the US and Germany, Livneh revealed how the error-prone repair works. The team found that such repair proceeds in two steps and requires two types of enzymes, belonging to the family of enzymes called DNA polymerases, which synthesize DNA. First, one repair enzyme, "the inserter," does its best to fit in a genetic "letter" into the gap, opposite the damaged site in the DNA molecule; several enzymes can perform this initial step, which often results in the insertion of an incorrect genetic letter. Next, another enzyme, "the extender," helps to restore regular copying of DNA by attaching additional DNA letters after the damaged site; only one repair enzyme is capable of

performing this vital second step. These findings were published recently in the *EMBO Journal*.

Understanding how this major form of DNA repair works can have significant clinical implications. Since defects in this process increase the risk of cancer, clarifying its nuts and bolts might one day make it possible to enhance it in people whose natural DNA repair is deficient. In addition, manipulating this mechanism can improve the effectiveness of cancer drugs. Cancer cells can resist chemotherapy by exploiting their natural repair mechanisms, and blocking these mechanisms may help overcome this resistance, leading to a targeted destruction of the cancerous tumor. ■

Prof. Zvi Livneh's research is supported by the Helen and Martin Kimmel Institute for Stem Cell Research; the estate of Lore F. Leder; and Esther Smidof, Geneva, Switzerland. Prof. Livneh is the incumbent of the Maxwell Ellis Professorial Chair in Biomedical Research.

For the scientific paper, please see: <http://www.nature.com/emboj/journal/v28/n4/full/emboj2008281a.html>

True Grit

Sea urchin digging teeth are designed to stay sharp

Sea urchins dig themselves hiding holes in the limestone of the ocean floor using teeth that don't go blunt. Weizmann Institute scientists have now revealed their secrets, which might give engineers insights into creating ever-sharp tools or mechanical parts.

The urchins dig holes to fit their globular bodies using their five teeth,

which, like those of rodents, are ground down at the tip but continue to grow on the other end throughout the animals' lives. The amazing part, however, is that the teeth, which need to be harder and stronger than the rocky limestone being dug out, are themselves made almost entirely of calcite – the same calcite that makes up much of the limestone. How

is this possible? In a series of studies spanning more than a decade, Profs. Stephen Weiner and Lia Addadi of the Weizmann Institute's Structural Biology Department have discovered that the urchins' secret lies in a combination of ingenious design strategies. The latest of these studies, conducted with postdoctoral fellow Dr. Yurong Ma and

graduate student Yael Politi and in collaboration with Prof. Pupa Gilbert and Dr. Rebecca Metzler of the University of Wisconsin, Drs. Barbara Aichmayer, Oskar Paris and Peter Fratzl from the Max Planck Institute of Colloids and Interfaces in Potsdam, Germany, and Dr. Anders Meibom from Muséum National D'Histoire Naturelle in Paris, France, was reported recently in the *Proceedings of the National Academy of Sciences (PNAS)*, USA.

The scientists found that the sea urchins' teeth contain crystals of magnesium calcite, which are smaller, harder and denser than those of pure calcite; they are concentrated at the grinding tip of the tooth, particularly in the tip's center, where the most force is being exerted in the course of grinding. What holds these crystals at the center of the tip is a matrix of larger and softer calcite crystals. While in most such materials a matrix of hard fibers contains a softer filling, the reverse is true for the urchins'

tooth: a matrix of relatively soft calcite fibers holds the harder magnesium calcite crystals, which allows these crystals to spread over the entire surface of the tooth. The presence of magnesium calcite crystals acts like sand paper that helps to grind the rock down.

In the latest study, the researchers used X-ray photoelectron emission spectromicroscopy and other high-resolution imaging methods to uncover yet another amazing structural feature of sea urchin tooth design. They found that all the crystalline elements that make up the tooth are aligned in two different arrays, and that these arrays are "interdigitated," or interlocked like the fingers of folded hands, just at the tip of the tooth where most of the wear occurs. The scientists believe that interlocking produces a notched, serrated ridge resembling that of a carpenter's file. This ridge is self-sharpening: as the tooth is being ground down, the crystalline layers break in such a way that the ridge always stays corrugated. ■

Prof. Lia Addadi's research is supported by the Clore Center for Biological Physics; the Ilse Katz Institute for Material Sciences and Magnetic Resonance Research; the Helen and Martin Kimmel Center for Nanoscale Science; the Helen and Milton A. Kimmelman Center for Biomolecular Structure and Assembly; and the Carolito Stiftung. Prof. Addadi is the incumbent of the Dorothy and Patrick Gorman Professorial Chair.

Prof. Stephen Weiner's research is supported by the Kekst Family Center for Medical Genetics; the Helen and Martin Kimmel Center for Archaeological Science; the Helen and Milton A. Kimmelman Center for Biomolecular Structure and Assembly; and the estate of George Schwartzman. Prof. Weiner is the incumbent of the Dr. Walter and Dr. Trude Borchardt Professorial Chair in Structural Biology.

For the scientific paper, please see: <http://www.pnas.org/content/106/15/6048.full?sid=39c9feb7-911b-4679-bc95-f752b74e0dcd>

Weizmann Institute Scientists Show

White Blood Cells Move like Millipedes

How do white blood cells – immune system "soldiers" – get to the site of infection or injury? To do so, they must crawl swiftly along the lining of the blood vessel – gripping it tightly to avoid being swept away in the blood flow – all the while searching for temporary "road signs" made of special adhesion molecules that let them know where to cross the blood vessel barrier so they can get to the damaged tissue.

In research recently published in the journal *Immunity*, Prof. Ronen Alon and his research student Ziv Shulman of the Weizmann Institute's Immunology Department show how white blood cells advance along the length of the endothelial cells lining the blood vessels. Current opinion maintains that immune cells advance like inchworms, but Alon's new findings show that the rapid movement of the white blood cells is more like that of millipedes. Rather than sticking front and back, folding and extending to push itself forward, the cell creates numerous tiny "legs" no more than a micron in length – adhesion points, rich in adhesion molecules

(named LFA-1) that bind to partner adhesion molecules present on the surface of the blood vessels. Tens of these legs attach and detach in sequence within seconds, allowing them to move rapidly while keeping a good grip on the vessels' sides.

Next, the scientists turned to the Institute's Electron Microscopy Unit. Images produced by scanning and transmission electron microscopes, taken by Drs. Eugenia Klein and Vera Shinder, showed that upon attaching to the blood vessel wall, the white blood cell legs "dig" themselves into the endothelium, pressing down on its surface. The fact that these legs – which had been thought to appear only when the cells leave the blood vessels – are used in crawling the vessel lining suggests that they may serve as probes to sense exit signals. The researchers found that the shear force created by the blood flow was necessary for the legs to embed themselves. Without the thrust of the rushing blood, the white blood cells couldn't sense the exit signals or get to the site of the injury. These results explain Alon's

previous findings that the blood's shear force is essential for the white blood cells to exit the blood vessel wall. The present study suggests that shear forces cause their adhesion molecules to enter highly active states. The scientists believe that the tiny legs are trifunctional: Used for gripping, moving and sensing distress signals from the damaged tissue.

In future studies, the scientists plan to check whether it is possible to regulate aggressive immune reactions (such as in autoimmune diseases) by interrupting the "digging" of immune cell legs into the endothelium. They also plan to investigate whether cancerous blood cells metastasize through the blood stream using similar mechanisms in order to exit the blood vessels and enter different tissues. ■

Prof. Ronen Alon's research is supported by the De Benedetti Foundation-Cherasco 1547. Prof. Alon is the incumbent of the Linda Jacobs Chair in Immune and Stem Cell Research.