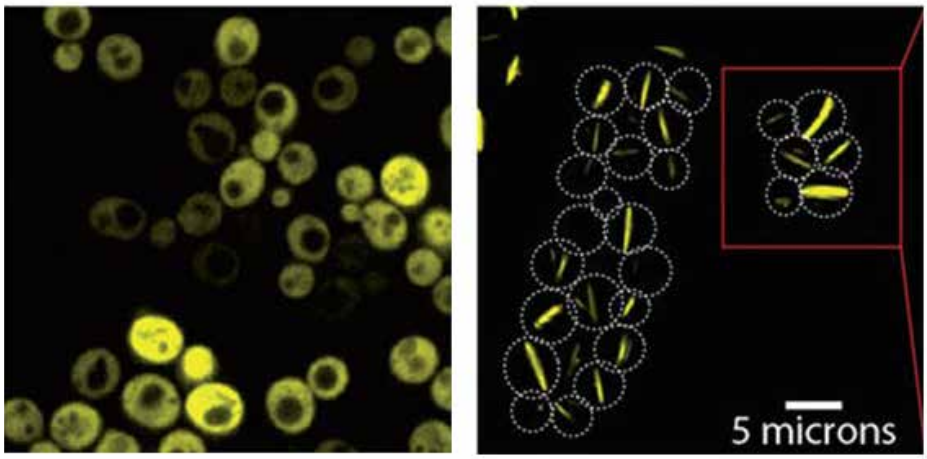
מכון ויצמן למדע
WEIZMANN INSTITUTE OF SCIENCE
Science Tips

Media Relations Department
Tel: 972-8-934-3852 / 56 Fax: 972-8-934-4132
http://wis-wander.weizmann.ac.il news@weizmann.ac.il
August 2017

Lego Proteins Revealed

Self-assembling protein complexes based on a single mutation could provide scaffolding for nanostructures

When hemoglobin undergoes just one mutation, these protein complexes stick to one another, stacking like Lego blocks to form long, stiff filaments. These filaments, in turn, elongate the red blood cells found in sickle-cell disease. For over 50 years, this has been the only known textbook example in which a mutation causes such filaments to form. According to Dr. Emmanuel Levy and his group in the Weizmann Institute of Science's Structural Biology Department, Lego-like assemblies should have formed relatively frequently during evolution. Could this assembly method be common, or even easy to reproduce? Their answer, which was recently published in *Nature*, may have implications for both biological research and nanoscience.



Yeast cells producing a bacterial symmetric protein complex with eight units. When it is not mutated (left), the complex diffuses freely inside the cell, but a single mutation (right) triggers its assembly into long filaments

If the researchers reproduced the phenomenon of sickle-cell filaments so easily in the lab, why is it not seen more in biomedical research?

Hemoglobin and a fair number of other protein complexes are symmetric: made of identical units. And since identical units are produced from the same gene, each genetic mutation is repeated multiple times in the complex. Mutations that create sticky patches and are repeated on opposite sides of the complex can induce the proteins to stack into long protein fibers. Unlike amyloid-like protein fibers, the complexes in these stacks do not change shape or unfold in order to assemble.

The stickiness occurs because the mutation substitutes an amino acid that is normally hydrophilic – "water-loving" – with one that is hydrophobic – "water-hating." In the watery environment in which proteins move, the hydrophobic regions on those proteins prefer to interact with one another, like foam bubbles in water.

In their experiments, Levy and his group, including Hector Garcia-Seisdedos, Charly Empereur-Mot (who is now at Conservatoire National des Arts et Métiers in Paris) and Nadav Elad of the Weizmann Institute's Chemical Research Support Department, began with an ultra-symmetric protein complex made up of eight identical units. They followed just one rule for mutating the proteins: Switch a hydrophilic amino acid with a hydrophobic, "sticky," one.

The team initially created proteins with three mutations to two different sticky amino acids and observed Lego-like self-assembly in both cases. Investigating further, the team experimented with each mutation individually and found that one was capable, on its own, of producing the long filaments.

So, are mutations that only do one thing – increase the stickiness of the protein's surface – likely to induce Lego-like self-assembly? The researchers mutated 11 additional proteins known to form symmetric complexes – creating 73 different mutations in all – and produced them in baker's yeast cells, adding a fluorescent protein "label" to enable their visualization. In 30 of these variations, the researchers observed behavior that suggested self-assembly: Around half of these had stacked into long filaments, while the other half were bunched together in a more amorphous way, forming "foci."

If the researchers reproduced the phenomenon of sickle-cell filaments so easily in the lab, why is it not seen more in biomedical research? Levy

>>>

proposes two answers: Firstly, the team revealed that naturally symmetric proteins evolved to have extra hydrophilic amino acids on their surfaces, thus minimizing the risk of self-assembly. Secondly, says Levy, researchers probably see more Lego assemblies than they think: "Now that researchers know they can evolve so readily, they may look at foci more carefully and see many more biologically relevant Lego-like assemblies."

"Also," he adds, "the filaments are produced so easily in the yeast, they could be good candidates for the scaffolding of nanostructures. Our study was unique in that it did not require complex computational design, nor did we have to scan thousands of mutations to find the one we wanted. We simply started with an existing structure and found a simple strategy to induce the assembly of filaments."

Dr. Emmanuel Levy's research is supported by the David and Fela Shapell Family Foundation INCPM Fund for Preclinical Studies; the Henry Chanoch Krenter Institute for Biomedical Imaging and Genomics; the Louis and Fannie Tolz Collaborative Research Project; the Richard Bar Laboratory; and Anne-Marie Boucher, Canada. Dr. Levy is the incumbent of the Recanati Career Development Chair.

http://www.nature.com/nature/journal/v548/n7666/full/nature23320.html?foxtrotcallback=true

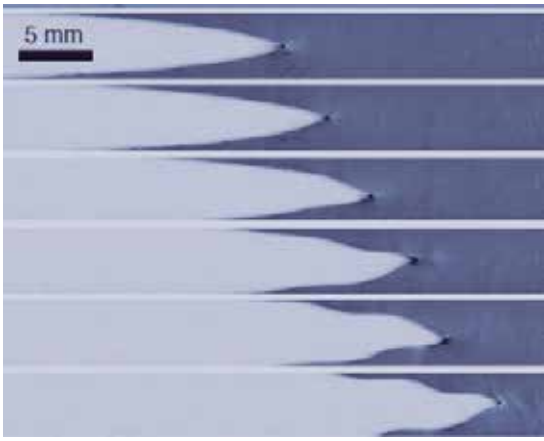
The Breaking Point

It is said that a weak link determines the strength of the entire chain. Likewise, defects or small cracks in a solid material may ultimately determine the strength of that material – how well it will withstand various forces. For example, if force is exerted on a material containing a crack, large internal stresses concentrate on a small region near the crack's edge. When this happens, a failure process is initiated, and the material might begin to fail around the edge of the crack, which could then propagate, leading to the ultimate failure of the material.

They occur in the same way in different materials and under different conditions

What, exactly, happens right around the edge of the crack, in the area in which those large stresses are concentrated? Prof. Eran Bouchbinder of the Weizmann Institute of Science's Chemical Physics Department, who conducted research into this question together with Dr. Chih-Hung Chen and Prof. Alain Karma of Northeastern University, Boston, explains that the processes that take place in this region are universal – they occur in the same way in different materials and under different conditions. "The most outstanding characteristic we discovered," says Bouchbinder, "is the nonlinear relationship between the strength of the forces and the response taking place in the material adjacent to the crack. This nonlinear region, which most studies overlook, is actually fundamentally important for understanding how cracks propagate. Most notably, it is intimately related to instabilities that can cause cracks to propagate along wavy trajectories or to split, when one would expect them to simply continue in a straight line."

By investigating the forces at play near the crack's edge, Bouchbinder and his colleagues developed a new theory – published recently in *Nature Physics* – that will enable researchers to understand, calculate and predict the dynamics of cracks under various physical conditions. This theory may have significant implications for materials physics research and for understanding the ways in which materials fail.



The trajectory of a crack tip, showing one cycle of oscillation. The horizontal wavy line shows the trajectory of the crack tip

Islands of softness

Exploring a different topic, in a paper that recently appeared in the *Proceedings of the National Academy of Sciences, USA, (PNAS),* Bouchbinder and a group of colleagues investigated the fundamental properties of the "glassy state" of matter. The glassy state can exist in a broad range of materials if their liquid state is cooled quickly enough to prevent them taking on an ordered, crystalline state. Glasses are thus disordered, or amorphous, solids and include, for example, window glasses, plastics, rubbery materials and amorphous metals. Even though these materials are all around us and find an enormous range of applications, understanding their physical properties has been extremely challenging, owing, in large part, to the lack of tools for characterizing their intrinsically disordered structures and characterizing how these structures affect the materials' properties. Dr. Jacques Zylberg of Bouchbinder's group, Dr. Edan Lerner of the University of Amsterdam, Dr. Yohai Bar-Sinai of Harvard University (a former PhD student of Bouchbinder's), and Bouchbinder found a way to identify particularly soft regions inside glassy materials. These "soft spots," which are identified by measuring the local thermal energy across the material, were shown to be highly susceptible to structural changes when force is applied. In other words, these soft spots play a central role when glassy materials deform and irreversibly flow under the action of external forces. The theory developed by the researchers thus brings us a step closer to understanding the mysteries of the glassy state of matter.

Prof. Eran Bouchbinder's research is supported by the Rothschild Caesarea Foundation; and Paul and Tina Gardner, Austin, TX.

https://www.nature.com/nphys/journal/vaop/ncurrent/full/nphys4237.html

http://www.pnas.org/content/114/28/7289.full?sid=1be2e753-501f-4eca-811b-5befda22b1df

New Years for Researchers

For one night only, the Weizmann Institute of Science will open its doors to the public

Ever wanted to know how to fix a broken heart? What a scratch, pneumonia and soil pollution have in common? Why insects could be the food of the future? Researchers Night at the Weizmann Institute of Science is an evening dedicated to science for everyone – to answering every and all questions about science.

Researchers Night has been taking place annually at the Weizmann Institute of Science since 2006, as part of the European Union Researchers Night event that takes place in hundreds of sites all over Europe. It occurs within a nation-wide framework of activities at academic research institutes and science museums, supported by the Israeli Ministry of Science, Technology and Space. Researchers Night at the Weizmann Institute of Science is organized by the Davidson Institute of Science Education, the educational arm of the Weizmann Institute of Science.

This year's Researchers Night theme is Humanity@2050, and it will take place just one night before the eve of Rosh Hashana, the Jewish New Year. By opening its doors to the public, the Weizmann Institute of Science is hoping to help answer one big question: Just what do all of its scientists do in their labs? The public is invited to partake of lectures and hands-on sessions, exhibits and demonstrations, tours of labs and a visit to the Clore Garden of Science.

> Prof. Ada Yonath will explain why some of the most amazing discoveries in medicine have been snatched from the brink of "bankruptcy

Nobel Laureate Prof. Ada Yonath will explain why some of the most amazing discoveries in medicine have been snatched from the brink of "bankruptcy;" Prof. Tzachi will talk about evolution as you've never heard it before; Dr. Ulyana Simanovich will speak about worms and mice and what they teach us; Prof. Dan Yakir will ask whether planting forests is the best way to alleviate global warming; Prof. Varda Rotter will give us a peek into the cancer genome; Prof. Eli Arama will talk about cells that commit suicide; and many other scientists will be present to talk about their latest forays into the forefront of global science.

The activities will commence at 17:00, Sept. 19, 2017, and continue until late in the evening in the auditoria, halls and open spaces of the campus. These are suitable for children, youth and adults. All the events and activities are free of charge, but some may require registration on the site bellow.

http://davidson.weizmann.ac.il/programs/2017