GERMAN CANCER RESEARCH CENTER
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How Aggregated Proteins Can Return to Their Original Shape

Anybody knows the process that happens when you cook an egg: The initially liquid and transparent egg white turns solid and opaque. Heidelberg scientists from the Center for Molecular Biology (ZMBH) at Heidelberg University and the German Cancer Research Center (DKFZ) have now discovered and unraveled a repair system used by cells to revert this protein aggregation. Experts from the Heidelberg Institute for Theoretical Studies (HITS) also participated in the research project. The scientists have now reported their research results in two simultaneously published articles in the specialist journal "Nature Structural and Molecular Biology".

Proteins are made of long chains of amino acids. In order to perform their often vital functions, each chain of amino acids must fold into a particular three-dimensional structure. If growth conditions change, such as by a rise in environmental temperature, proteins may lose their structure and unfold. Then there is a danger of the unfolded protein chains clumping together. "Such aggregated proteins can no longer perform their tasks", says Prof. Dr. Bernd Bukau, who heads a joint research department of the Center for Molecular Biology (ZMBH) at Heidelberg University and the German Cancer Research Center (DKFZ). "This loss of function can lead to cell death as it does, for example, in neurodegenerative diseases such as Alzheimer's and Parkinson's or in aging processes."

However, aggregation does not necessarily have to be the end of a protein's life cycle. "Cells have repair systems called molecular chaperones, which can even dissolve and refold aggregated proteins," says Associate Professor (PD) Dr. Axel Mogk, who is also a member of both ZMBH and DKFZ. A team of two chaperones known as Hsp70 and Hsp100 carry out the "repair". The Heidelberg scientists were able to show that Hsp70 regulates the activity of the Hsp100 chaperone using an inbuilt molecular switch.

This switch is initially in "off" position, meaning that it curbs energy consumption and hence the activity of Hsp100. As soon as team partner Hsp70 spots an aggregated protein, it throws the switch into "on" position, thereby activating Hsp100 on the spot. In this state, the "motor" of the ring-shaped Hsp100 protein starts and can pull out individual chains from the protein aggregate. The disaggregated, unfolded protein then has a chance to reassume its original structure and become functional again. The Heidelberg scientists could also show that the inbuilt switch plays an essential role in this complicated repair system, because its loss in permanently active Hsp100 variants leads to cell death.

The research work is a project of the DKFZ-ZMBH Alliance, which is a strategic collaboration of the German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ) and the Center for Molecular Biology (ZMBH) at Heidelberg University. The Heidelberg Institute for Theoretical Studies (HITS) focuses on new theoretical approaches towards interpreting the rapidly increasing amount of experimental data.

Original publications:

F. Seyffer, E. Kummer, Y. Oguchi, J. Winkler, M. Kumar, R. Zahn, V. Sourjik, B. Bukau & A. Mogk: Hsp70 proteins bind Hsp100 regulatory M domains to activate AAA+ disaggregase at aggregate surfaces, Nature Structural & Molecular Biology, 18 November 2012, doi: 10.1038/nsmb.2442

Y. Oguchi, E. Kummer, F. Seyffer, M. Berynskyy, B. Anstett, R. Zahn, R.C. Wade, A. Mogk & B. Bukau: A tightly regulated molecular toggle controls AAA+ disaggregase, Nature Structural & Molecular Biology, 18 November 2012, doi: 10.1038/nsmb.2441

The German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ) with its more than 2,500 employees is the largest biomedical research institute in Germany. At DKFZ, more than 1,000 scientists investigate how cancer develops, identify cancer risk factors and endeavor to find new strategies to prevent people from getting cancer. They develop novel approaches to make tumor diagnosis more precise and treatment of cancer patients more successful. Jointly with Heidelberg University Hospital, DKFZ has established the National Center for Tumor Diseases (NCT) Heidelberg where promising approaches from cancer research are translated into the clinic. The staff of the Cancer Information Service (KID) offers information about the widespread disease of cancer for patients, their families, and the general public. The center is a member of the Helmholtz Association of National Research Centers. Ninety percent of its funding comes from the German Federal Ministry of Education and Research and the remaining ten percent from the State of Baden-Württemberg.

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