



Press Release

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Choice of molecular partners is no mere formality

A molecular helper influences clumping of the tau protein in Alzheimer's disease

Alzheimer's disease is triggered by the death of millions of neurons in the brain. A decisive part in this process is played by the tau protein, which clumps together in cells of affected brain regions. A molecular helper called heat shock protein (Hsp) 90 influences this aggregation by recognizing and binding tau. Scientists have now discovered that this choice of partner occurs according to principles fundamentally different from those generally observed among proteins. These findings provide a new approach for investigating the emergence of Alzheimer's disease. (*Cell*, February 28, 2014)

They miss appointments and forget places, find it harder to think and speak, and at some stage even simple movements become a challenge. Increasing numbers of people, particularly the elderly, are developing Alzheimer's disease. In Germany alone, there are 300,000 new cases every year. The course of the disease is irreversible, and ultimately patients need care and often become socially isolated. There is no effective treatment for this disease to date. Alzheimer's is caused by the million-fold death of neurons in the brain. In affected tissue clumped heaps of tau proteins are found, which contribute to malfunction of neurons and eventually to their death.

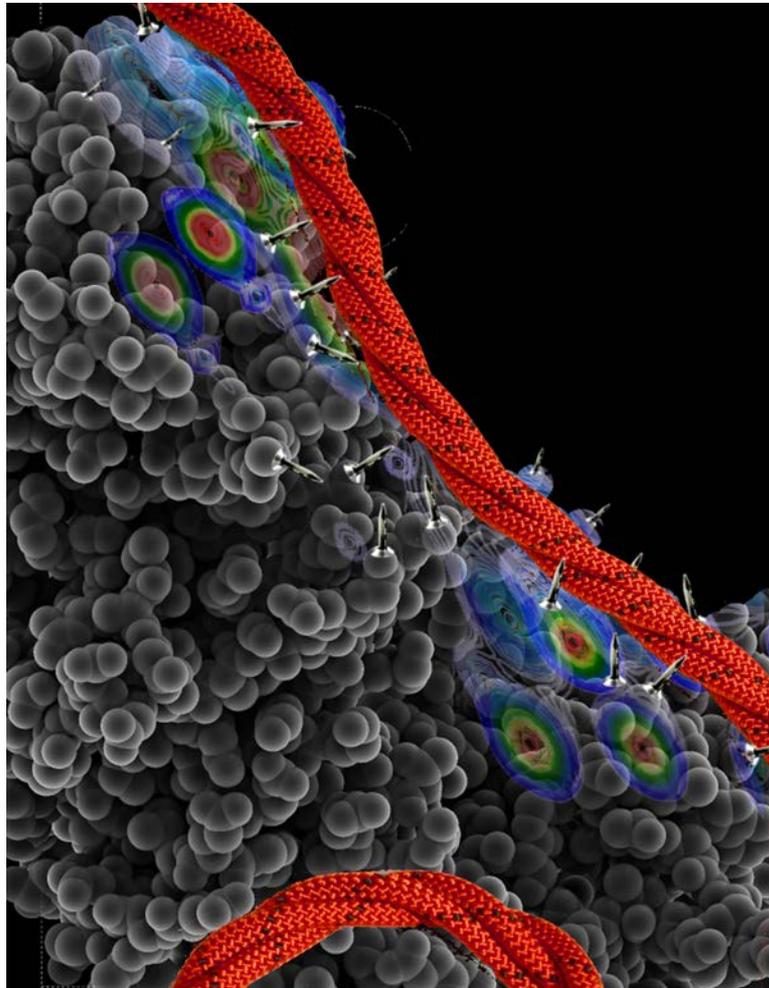
The tau protein, however, is not harmful in itself and actually even has a vital function in living cells. It binds to microtubules – scaffolding components of the cell structure – and thereby helps stabilize the cells. Only when a person develops Alzheimer's does tau occur in an altered state in neurons and clump together. But what triggers this devastating change?

An international team of scientists has now cast light on how a molecular helper called Hsp90 binds tau and how the two proteins "speak" to each other. This communication also influences tau's fate: whether it remains functional or heaps up to the detriment of the cell. By applying nuclear magnetic resonance spectroscopy the researchers have now analyzed the Hsp90-tau complex at high resolution.

Awkward partner

Tau is anything but easy to recognize for other proteins, as it is very unusual in a number of ways. In contrast to many other proteins, it does not need to adopt a particular shape to carry out its task

in the cell. In addition, it is extremely versatile. "As we have discovered, Hsp90 recognizes tau and probably also other partner proteins by a mechanism completely new to us scientists," Stefan Rüdiger of Utrecht University (the Netherlands) explains. The international team comprising scientists at Utrecht University, the German Center for Neurodegenerative Diseases (DZNE) in Göttingen and Bonn, the Max Planck Institute for Biophysical Chemistry (MPIbpc), the University Medical Center in Göttingen and the University of South Florida (USA), solved the structure of the Hsp90-tau complex in atomic detail.



The helper protein Hsp90 (gray) binds tau (red) with a big surface and many contacts. (Image: Rüdiger / Utrecht University)

Hsp90 belongs to the chaperone protein family whose members act as molecular folding assistants and also protect proteins from stress such as heat exposure. They can bind a large number of different proteins and tightly control if these are correctly folded and functioning. In contrast to other chaperones, however, Hsp90 does not have any barcode scanner-type region to recognize and bind its partner proteins. It is not at all clear to date how Hsp90 manages to find and bind all its different partners without such a scanner region.

Tau, in turn, has no part that would serve as a barcode, so Hsp90 "palpates" tau with a surface that is much bigger than the regions other chaperones use as barcode scanners. "With this previously unknown mechanism of partner selection, Hsp90 can recognize and bind a large number of completely different proteins, because, despite their variety, through the eyes of Hsp90 they all look the same," says Markus Zweckstetter, head of research groups at the DZNE, the MPIbpc, and the University Medical Center in Göttingen.

But what happens to the tau protein when it binds to Hsp90? "So far, we are unable to clearly tell whether it is harmful or beneficial for the protein, but we hope to solve this issue in our future research," Zweckstetter states.

Original publication

G. Elif Karagöz, Afonso M.S. Duarte, Elias Akoury, Hans Ippel, Jacek Biernat, Tania Morán Luengo, Martina Radli, Tatiana Didenko, Bryce A. Nordhues, Dmitry B. Veprintsev, Chad A. Dickey, Eckhard Mandelkow, Markus Zweckstetter, Rolf Boelens, Tobias Madl, Stefan G.D. Rüdiger: Hsp90-Tau complex reveals molecular basis for specificity in chaperone action. *Cell* **156**, 963-974, doi: 10.1016/j.cell.2014.01.037 (2014).

Further information

www.dzne.de/en/sites/goettingen/forschergruppen/zweckstetter.html – website of the Research Group Structural Biology in Dementia, German Center for Neurodegenerative Diseases (DZNE)

www.mpibpc.mpg.de/en/zweckstetter – website of the Research Group Structure Determination of Proteins Using NMR, Max Planck Institute for Biophysical Chemistry

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