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New structural data on talin explain self-inhibitory mechanism

Researchers at the Max Planck Institute of Biochemistry have elucidated the entire structure of the talin protein with the help of cryo-electron microscopy. The new findings explain the protein's self-inhibitory mechanism.

- **Defective cellular adhesion plays a central role in cancer and immune reactions**
- **Talin is one of the key proteins involved in the machinery of cellular adhesion**
- **The entire structure of talin has been determined with the help of cryo-electron microscopy**
- **Now the protein's regulation mechanism can be explained**

All complex organisms are made up of cells that are in contact with each other or with structures in intercellular spaces. Cells have contact points on their surface that enable them to maintain physical contact with their environment. However, these connections are dynamic, not static. A finely regulated process of cellular attachments and detachments is particularly important during cell migration, cell development, immune responses and blood clotting. For this reason, the contact points form an elaborate protein machinery.

Talin and integrin, two key proteins in the cellular adhesion machinery, have been the subject of much research in recent years. Together with her team, Naoko Mizuno, head of the "Cellular and Membrane Trafficking" Research Group at the Max Planck Institute of Biochemistry, has now elucidated the structure and regulatory mechanism of talin with the help of cryo-electron microscopy. "Although talin is recognized as key for the cell migration, its regulation was enigmatic as the architecture of the molecule as a whole was unknown," Mizuno says.

Dirk Dedden, lead author of the study, comments: "We've focused on analyzing the protein as a whole. Using a variety of modern biophysical techniques, we've discovered which environmental

conditions cause the protein to alter its state reversibly." Thanks to controllable laboratory conditions, the scientists have now been able to determine the protein's precise molecular structure by means of cryo-electron microscopy.

Talin, like a mechanical spring, is spherical in shape in its inactive form and oblong in its active state. The researchers have now been able to identify which areas of inactive talin are shielded from the environment in its spherical self-inhibitory state. This means that neighbouring proteins are unable to interact with the molecule, and the cell itself is unable to adhere to surrounding tissue. In its elongated active form, the molecule acts as a binding platform for neighbouring proteins, which furthermore promotes attachment of the cell to its surrounding structures.

Naoko Mizuno explains: "Given that the cellular adhesion process no longer functions properly in some diseases, notably cancer, our results will hopefully have long-term medical benefits. Talin is known to activate integrin, and integrin is a well-known target for some anticancer drugs. We hope that an understanding of the regulatory process of the adhesion mechanism will shed light on disease processes and lead to new treatments."

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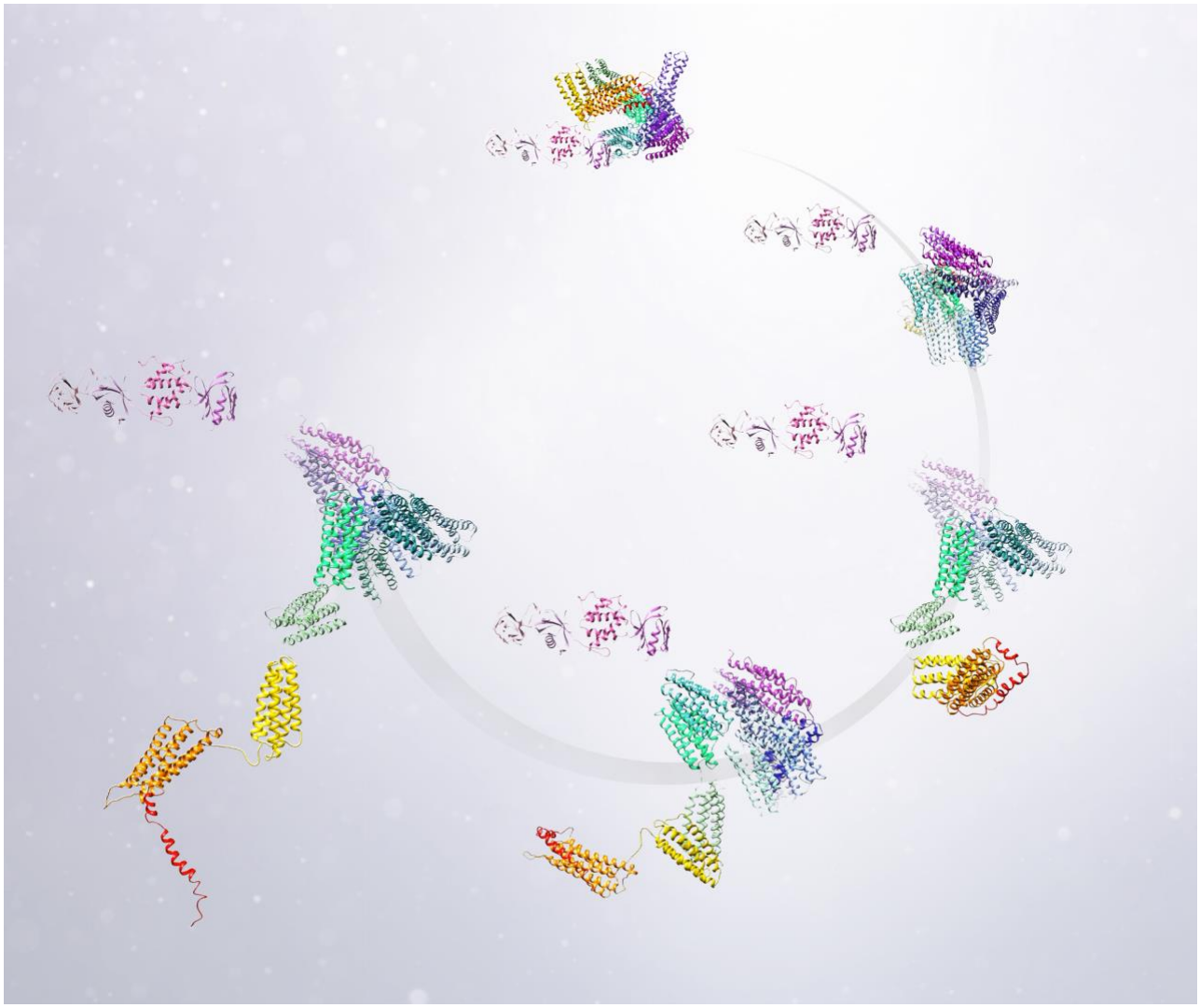

Caption: Regulatory mechanism of talin: from the spherical, inhibited state to the elongated and active form
Picture: ©Naoko Mizuno, MPI of Biochemistry

Original publication

D. Dedden, S. Schumacher, C. F. Kelley, M. Zacharias, C. Biertümpfel, R. Fässler, N. Mizuno: The architecture of talin1 reveals an autoinhibition 1 mechanism. *Cell*, September 2019
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About Naoko Mizuno

Naoko Mizuno studied biophysics at the University of Tokyo in Japan. In 2005, she received her PhD from the University of Texas Southwestern Medical Center in the USA. She did her postdoctoral

work in the Laboratory of Structural Biology at the National Institutes of Health in the USA. Since 2013, Mizuno has been a group leader at the MPIB. She has received various awards and research grants, among them the EMBO Young Investigators award and an ERC consolidator grant.

About the Max Planck Institute of Biochemistry

The Max Planck Institute of Biochemistry (MPIB) belongs to the Max Planck Society, an independent, non-profit research organization dedicated to top level basic research. As one of the largest Institutes of the Max Planck Society, 850 employees from 45 nations work here in the field of life sciences. In currently eight departments and about 25 research groups, the scientists contribute to the newest findings in the areas of biochemistry, cell biology, structural biology, biophysics and molecular science. The MPIB in Munich-Martinsried is part of the local life-science-campus where two Max Planck Institutes, a Helmholtz Center, the Gene-Center, several bio-medical faculties of two Munich universities and several biotech-companies are located in close proximity. http://www.biochem.mpg.de

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