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News Release

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New basis for drug development:

Structure determination of biomolecules in their natural environment

Scientists from the Helmholtz Zentrum München and the Technische Universität München (TUM) under the direction of Prof. Michael Sattler have developed a new strategy allowing them to determine the spatial structure of biomolecules in solution. The method is flexible and generally applicable to obtaining structural information for signal forwarding pathways in the cell or in the regulation of gene expression. The current online issue of the prestigious scientific journal Angewandte Chemie reports on their results.

Most larger proteins have complex spatial structures in which various compact subunits are connected by flexible linkers. There is sufficient space between these subunits for solution molecules and reactants. However, in protein crystals used for the classical structure elucidation with X-rays, the subunits are much more tightly packed. A number of questions on the interaction of these subunits – questions relevant to understanding the mechanisms of diseases – can thus not be answered.

The team headed by Prof. Michael Sattler, director of the Institute of Structural Biology at the Helmholtz Zentrum München and head of the Bavarian NMR Center at the TU München, combined a number of existing approaches into a single strategy, allowing the scientists to determine the spatial structure of biomolecules in solution. The basis for this technique is biomolecular NMR spectroscopy (nuclear magnetic resonance). “NMR spectroscopy is the only method that allows us to determine atomic details in the spatial structure of biomolecules in solutions,” explained Prof. Sattler.

Because of their size, when proteins or protein complexes are analyzed using NMR one initially obtains a number of overlapping signals that are hardly suitable for processing. Thanks to a four-step strategy that the scientists integrated into an existing software program for the evaluation of NMR measurements, Michael Sattler and his team can now separate the signals and thus obtain a structure that closely resembles reality.

In the first step of the new procedure the scientists collect existing structural information for the subunits. This information is obtained from X-ray structure analysis, for instance. The next steps determine how these subunits are spatially oriented with respect to each other. Two

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different types of information are used for this purpose, both of which are obtained through NMR experiments. So-called dipolar residual couplings provide information on the relative orientation of the individual subunits of the complex.

In the next step the scientists introduced nitroxyl groups (molecules containing an unpaired electron) at various positions in the protein. These set off so-called paramagnetic relaxation enhancements, enabling the scientists to measure larger distances between the subunits and thereby deduce the three-dimensional structure of the protein complex.

The team conducted the procedure on two structural subunits of the human splicing factor U2AF65. Splicing factors are decisive in regulating gene expression and enable the formation of different proteins from a single gene, among other things. The structure of the complex can then be calculated by skillfully combing the various NMR data. The results confirmed that the structure in solution differs significantly from the structure determined using X-ray crystallography.

“Our method is generally applicable to a wide variety of protein complexes, even when they are very large or comprise numerous subunits,” emphasized Prof. Sattler. “This allows us to examine biological regulation mechanisms in which weak and transient interactions play an important role.” Proteins are not rigid structures – they are flexible, allowing them to bind and release reactants. These dynamic effects are essential for the molecular identification of countless biological processes.

As such, the new procedure is particularly useful in research: The characterization of the structure and interaction of proteins and reactants provides information on the ways in which metabolic processes evolve and how diseases develop, and thus provides a scientific basis for the development of new medication.

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