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News Release

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Mystery about recognition of unfolded proteins solved:

The lock shapes the key

Proteins typically recognize each other by their specific three-dimensional structure. If the key fits in the lock, a reaction can take place. However, in some cases the key does not have a specific shape at the onset of the reaction. Chemists at the Technische Universität München (TUM) and the Max Planck Research Unit for Enzymology of Protein Folding (Halle/Saale) have now shown how this recognition can work. Their results will appear in the Proceedings of the National Academy of Science (PNAS) this week.

Interactions between proteins are of fundamental importance for various processes in all living cells. In order to carry out any biological function, proteins must first fold into a specific three-dimensional shape. A number of reactions have been described in recent years, where one of the interaction partners does not adopt its active structure until the actual binding process occurs. It was a great mystery, how the binding partners could recognize such unstructured proteins.

Scientists led by Professor Thomas Kiefhaber (TUM) posed the question of whether local properties are sufficient for the recognition or whether the unstructured binding partner first has to adopt a specific spatial structure. Possible candidates were regularly structural elements such as α-helices or β-pleated sheets, in which internal hydrogen bonds are formed.

In collaboration with Professor Gunter Fischer's research group at the Max Planck Research Unit for Enzymology of Protein Folding Halle/Saale, the scientists developed a novel method for observing the formation of individual hydrogen bonds in the course of a folding and binding process.

As model system they used the enzyme ribonuclease S, which in its active form comprises the S-protein and the α-helical S-peptide. The S-protein has a defined three-dimensional shape, whereas the S-peptide on its own is initially unfolded. The scientists attempted to determine whether the S-protein recognizes the unstructured S-peptide or a small fraction of peptide molecules in their helical conformation. To this end, single oxygen atoms of the peptide bonds were replaced by sulfur atoms via chemical protein synthesis, which destabilizes individual hydrogen bonds.

Time-resolved measurements of the binding process of the modified peptides have shown that the hydrogen bonds in the S-peptide, which are indicative for α-helical structure, only form after binding to the S-protein. This means that the α-helical structure does do not play a role in the recognition process. Protein-protein recognition in this case is mediated by hydrophobic

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interactions between the S-protein and two spatially well-defined areas on the unstructured S-peptide.

These results are of fundamental importance for understanding the mechanism of protein-protein interactions. In the future, this method can be applied to other systems in order to monitor structure formation during protein folding.

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Publication:

Mapping backbone and side-chain interactions in the transition state of a coupled protein folding and binding reaction, Annett Bachmann, Dirk Wildemann, Florian Praetorius, Gunter Fischer, and Thomas Kiefhaber
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