The lock shapes the key: Mystery about recognition of unfolded proteins solved

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Proteins normally recognize each other by their specific 3-D structure. If the key fits in the lock, a reaction can take place. However there are reactions at the onset of which the key does not really have a shape. German chemists at the Technische Universitaet Muenchen and the Max Planck Research Unit for Enzymology of Protein Folding (Halle/Saale) have now shown how this might work. Their results will appear in *PNAS* this week.

Interactions between proteins are of fundamental importance for a number of processes in virtually every living cell. However, in order for the proteins to carry out any biological function, they must first assume their specific three-dimensional shape. A number of reactions have been described in recent years, where one of the interaction partners does not assume its active structure until the actual binding process commences. It was still a great mystery, though, how the binding partners could actually recognize such unstructured proteins.

Scientists led by Professor Thomas Kiefhaber (TUM) posed the question of whether local properties are sufficient for the recognition to take place or whether the unstructured binding partner first had to assume a specific spatial structure. Possible candidates were regularly structural elements such as coiled 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 binding process.

The model system was the enzyme ribonuclease S, which in its active form comprises the S-protein and an α-helical S-peptide. While the S-protein has a defined three-dimensional shape, 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, the oxygen atoms in the peptide bonds were replaced by sulfur atoms via chemical protein synthesis, causing individual hydrogen bonds to become destabilized.

Time-based measurements of the binding process of the altered peptide have now shown that the hydrogen bonds in the S-peptide, and as such in the α-helical structure, do not form until after the bonding to the S-protein. Thus, they cannot play a role in the recognition process. Protein-protein recognition in this case takes place via hydrophobic interaction of the S-protein with two spatially clearly defined areas of 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 used to examine in detail the structure formation in proteins in other systems, as well.

More information: 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 *PNAS*, Early Edition, Publikation Online in der Woche vom 14.02.2011, www.pnas.org/cgi/doi/10.1073/pnas.1012668108

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