

DBT/ International Centre for Genetic Engineering and Biotechnology

Understanding the structure of an intermediate state during protein unfolding

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New Delhi, February 18: Proteins are key component of biological systems. It is very important to know their three-dimensional structure to understand functionality of cellular system and processes. The Process of Protein Folding, starts immediately at their birthplace (Ribosomes) and most proteins emerge as perfectly folded native structure at the end of their complete synthesis. However, there are few which require helper protein molecules called chaperone to correctly shape them. Different kinds of protein have different lifespan and at the end of it they are degraded to individual units with the help of another set of protein molecules. The process is called 'Protein Unfolding'. Both folding and unfolding processes are very specific, rapid and follow a well-defined path. Several test tube studies have demonstrated that proteins unfold under different physical and chemical conditions and refold to their native confirmation upon removal of such conditions. This helped the experimentalists to follow folding-unfolding pathways at a high spatial and time resolution and understand mechanisms. Difference in protein structure from normal may lead to several diseases such as muscular dystrophy disease. The key to understand origin of a disease is to understand protein (un)folding mechanism, which is still a challenge.

Dr. Neel Sarovar Bhavesh, a structural biologist at ICGEB has done studies to understand unfolding mechanism of RNA recognition pattern (RRM). He used a canonical RRM from a protein (ETR3) involved in muscular dystrophy disease to understand the unfolding mechanism of RRM containing protein. This is important as a similar pattern in another protein (TDP-43) aggregates and eventually leads to neuromuscular disease conditions due to formation of non-native structural elements. The studies were done and found that intermediate state has folded like structure but swollen and dynamics. It allows solvent to access its core more easily than the folded structure. The edges of secondary structural elements are the initiation sites of unfolding. Although the unfolded state is very dynamic and lacks any structural elements still it shows bias for certain structural tendency which appears like keeping a memory of their folded state.

It is believed that the atomic-resolution characterisation of unfolding pathway of a canonical RNA recognition motif is likely to help in understanding the unfolding events in other RRMs involved in disease causing conditions upon misfolding.

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