The Structure of Unstructured Proteins: A Multidisciplinary Approach

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The structural characterization of unfolded states of proteins has been traditionally linked to protein folding and protein stability studies. This interest has been recently renewed due to the discovery of a new family of proteins, the so-called Intrinsically Unfolded Proteins (IUPs), that plays relevant biological roles even though they lack tertiary structure. The inherent plasticity confers to IUPs the capability of performing very specialized tasks in vivo including a high specificity and low affinity recognition of partners. This property makes IUPs appropriate for signal transduction and cell regulation. In addition, some unstructured proteins have been linked to amyloidogenic diseases such as Alzheimer and Parkinson.

The inherent plasticity of IUPS places them beyond the reach of traditional structural biology methods that assume that the biophysical parameters measured arise from a well defined, rather rigid, structure. NMR is well suited for the study of flexible molecules. However, parameters such as chemical shifts or Residual Dipolar Couplings (RDCs) are averaged over all conformations accessible in solution. Therefore, new approaches are needed that account for this structural variability.

In this talk a general method for the structural characterization of IUPs will be presented [1]. It will be shown that this approach is able to describe the conformational sampling at residue level, probed by backbone RDCs. Important characteristics such as low populated structured regions and the presence of transient long-range interactions will be discussed using different examples. The relevance of complementary methods such as small-angle X-ray scattering (SAXS) or hydrodynamic measurements to characterize the overall dimensions of the ensemble will be presented.

[1] Bernadó, P.; Blanchard, L.; Timmins, P.; Marion, D.; Ruigrock, R.W.H.; Blackledge, M. *Proc. Natl. Acad. Sci. USA*, **2005**, *102*, 17002-17007.