NUS National University of Singapore | Department of Biological Sciences, Faculty of Science

BIOLOGY COLLOQUIUM

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NMR reveals order in disordered proteins

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Despite the accepted belief that protein function is encoded in the three dimensional (3D) structure of a protein Intrinsically Disordered (IDPs) have attracted a lot of attention over the last decade due to both their fascinating structural properties and their involvement in important physiological and pathological processes. The inherent structural flexibility of IDPs requires the application of appropriate experimental methods since X-Ray crystallography cannot access the distribution of conformational states of these proteins. Over the last decade an NMR based methodological framework has emerged to characterize the structural dynamics of IDPs. In particular, paramagnetic relaxation enhancement (PRE) has matured into a well-established technique to probe residual structures and local compaction of the polypeptide chain as well as long-range transient contacts, although the existence of concerted motions and cooperatively folded segments cannot be detected. To circumvent this problem we recently proposed a novel technique coined paramagnetic relaxation interference (PRI) based on cross-correlation effects between pairs of spin labels in doubly-labelled protein systems.

Additionally, 15N NMR spin relaxation is a rich source of information to characterize the dynamic behavior of globular proteins and employed to characterize protein backbone dynamics. A less commonly known approach uses cross-correlated NMR relaxation (CCR) to study structure and dynamics of proteins in solution. Cross-correlated relaxation arises from interference effects between the fluctuations of two different relaxation mechanisms, which are active simultaneously and in a correlated manner. These effects been shown to be a valuable source of information about structure and dynamics of proteins, since their concerted effect is related to their relative geometry. Typically cross-correlated interference effects can be observed between two different dipolar (D) interactions (D-D), two different chemical shift anisotropies (CSA-CSA) or between a dipolar and a chemical shift anisotropy (D-CSA) interaction. To resolve angular ambiguities of single cross-correlation rates a method has been suggested exploiting the simultaneous analysis of different complementary cross-correlation rates for the extraction of unambiguous and reliable dihedral angles along the protein backbone in folded proteins. Although the situation is more complex in IDPs it will be demonstrated that this approach is also feasible in conformationally flexible proteins. Given the sensitivity of CCR experiments to subtle structural changes, together with the diversity of CCR experiments, which are at the disposition of the investigator and which can be tailored to a specific structural or dynamic problem, it can be expected that CCR will be able to make a substantial contribution to the study of the dynamic nature of IDPs in solution.

Artwork by Ann Nee, DBS, NUS