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On the importance of intrinsically disordered segments in multidomain proteins: The example of the interplay between STAM2, AMSH and polyubiquitin chains

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Since more than three decades, structural biology has provided an impressive number of structures of folded proteins that allowed the understanding of their function. Recent studies on intrinsically disordered proteins (IDP) or intrinsically disordered segments (IDS) containing proteins have revealed that a specific fold is not necessary to establish a given interaction. Furthermore, multidomain proteins can simultaneously present well folded domains and highly flexible linkers that bestow a high flexibility to the entire protein. Such a flexibility allows to adopt a given structural organization and induce further interactions with possible multiple partners. Such IDS are now recognized as key players in the cell machinery, notably as mediator or modulator of protein-protein interactions or as signaling hub. As an example, we focus on the three domains construct VUS (VHS-UIM-SH3) of the STAM2 protein that harbors two flexible linkers of 20 amino acids. By means of NMR spin relaxation and SAXS, we show that these regions are highly flexible and that the complete protein could be described by an ensemble of conformations rather than a unique structure. The result is an exquisite propensity to interact with polyubiquitin chains through each of STAM2's domains. Indeed, Lys63 di-ubiquitin is binding to the VHS, UIM and SH3 domains of STAM2 with roughly the same affinity. At the same time, AMSH, a deubiquitinating enzyme is free to interact with the SH3 domain of STAM2 and outcompetes Lys-63 di-ubiquitin chains. It encourages us to propose a model where a specific structural organization between three different proteins allows the specific cleavage of polyubiquitin chains. This is rendered possible only by the high flexibility of the IDS of STAM2.

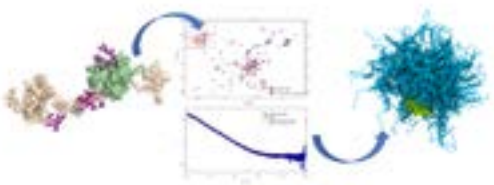

Figure 1: Combining NMR and SAXS allows the structural and dynamical characterization of IDS containing proteins

Biography

Olivier Walker has a strong expertise in NMR methodology and computational methods. More specifically, he has developed original approaches aiming at the determination of the structure and dynamics of polyubiquitin chains. Altogether, he can tackle some important questions raised in the field of life science by means of NMR, SAXS, SANS and computational approaches. He has also developed different programs related to the analysis of NMR spin relaxation and the determination of the relative orientation of different domains in multidomain proteins. More recently he has focused on different approaches aiming at the incorporation of NMR data into molecular dynamics simulations.

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