Study of the NCBD domain of the CREB-Binding Protein using NMR of Fluoro-prolines.

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Résumé

Transcriptional regulation relies on subtle equilibriums between regulatory proteins that are integrating various signals from the cell through chemical modifications or interactions with molecular partners. The underlying molecular mechanisms are characterized by the complexity of the interaction networks, the molecular architectures of the transcriptional complexes and their dynamical properties. The functional importance of this later is evidenced by a large representation of Intrinsically Disordered Region (IDR) in the sequence of the transcriptional regulators. One of the IDR sequence characteristics is the abundance of proline residues, either as part of a polyproline domain, or as part of a Xaa-Pro phosphorylation site. In this presentation, we present a chemical biology approach to study the role of proline in the dynamics of the CREB-Binding Protein. This protein contains a domain (NCBD) identified as a molten globule that is involved in the interaction with several partners. The substitution of two prolines of NCBD sequence by fluorinated prolines using chemical ligation chemistry (coll. Vladimir Torbeev, ISIS) was used to get insights on the role of these residues in the dynamical properties of the molten globule either in isolation or in complex with the P53 Trans-Activation Domain (TAD). This study revealed how the sequence context influences proline's conformational biases to achieve specific molecular properties.

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