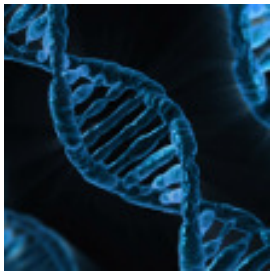

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The Role of MB0, MBI and MBII in Interaction and Dynamics of the Master Regulatory Transcription Factor c-Myc.

Balancing normal cell growth requires a maximum of molecular adaptability to respond easily and correctly to rapid changes in the cellular environment. A single protein may be required to interact with several hundred different partners, with maintained specificity but with built-in versatility in the response. Intrinsically disordered proteins (IDPs) proteins lack stable folded structure under native conditions but can interact simultaneously with multiple partners and/or binding sites, thus facilitating rapid biological response to transient signals. The oncoprotein c-Myc belongs to the IDP group of proteins and is an oncogenic master regulator overexpressed in more than half of human cancers, but characterizing its interactions are inherently difficult due to their short-lived nature. Located within the intrinsically disordered N-terminus part of c-Myc are the highly conserved so-called Myc boxes (MB0-IV), which are crucial for Myc function and interaction with other transcription factors. We have used BioID to identify several hundreds of c-Mycs dynamic interaction partners and used deletion mutants to identify MB0 and MBII as critical for tumor growth. Here, I will describe our recent progress in characterizing the structure and interactions of c-Myc focusing on MB0-II by nuclear magnetic resonance (NMR), small-angle x-ray scattering (SAXS) and protein crystallography. We will present first molecular data showing how these boxes interact with critical transcription factors as well as with each other in a highly specific but also highly dynamic manner, and how these interactions can be interrupted. Our ultimate aim is to provide a molecular platform for c-Myc inhibitor design.

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Track Classification : Dynamics of proteins in crowded and confined geometry