The N-Myc MB0-MBI region interacts specifically and dynamically with the N-lobe of Aurora kinase A

Johanna Hultman, Vivian Morad, Alexandra Ahlner & Maria Sunnerhagen.

Department of Physics, Chemistry and Biology, Division of Chemistry, Linköping University, Linköping, Sweden.

The intrinsically disordered MYC proteins are master regulators of cellular growth and function, but when deregulated they become cancer drivers. MYC-protein interactions are key to oncogenesis, and while disrupting such interactions would be of significant therapeutic benefit, the intrinsically disordered properties of MYC have dramatically hampered their characterization. Here, we apply an integrated structural biology approach to describe the structure and dynamics of the N-Myc–Aurora A complex, which is critical in neuroendocrine tumor progression. We reveal a functional interaction where multiple binding sites on N-Myc interact with the Aurora A N-lobe in a multivalent manner governed by residue clusters within the conserved MB0 and MBI motifs. We also show that N-Myc binding to the Aurora A N-lobe can be inhibited via small-molecule binding, providing opportunities for new therapeutical strategies to disrupt this interaction.