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Regulation of Myc-Max DNA binding in cancer

Content

Myc proteins are multifunctional, as they play a role in cell cycle progression, apoptosis, and cellular transformation processes. Deregulated Myc proteins lead to an unregulated expression of many genes that results in transforming normal cells into cancer cells. These proteins belong to the Myc family of transcription factors and comprise a large intrinsically disordered region, comprising conserved so-called Myc Box regions (MB0-MBIV), and a bHLHzip DNA-binding motif. These regions play an important role in Myc interactions with DNA and other transcription factors. Our research mainly focuses on the understanding of the interactions between Myc and its interaction partner proteins like Max. Uncontrolled Myc expression turns the Myc-Max heterodimer into an oncoprotein multimodular platform and acts as a key contributor to the development of numerous cancers.

In this work, we present the structure envelope of extended MYC(MBIV)-MAX and MAX-MAX dimers in complex with DNA, as described by SAXS and SANS. Existing crystal structures of Myc-Max and Max-Max dimers only included the bHLHzip DNA-binding motif without flanking regulatory regions. Our group has previously shown by CD that flanking regions of the Max bHLHZip core significantly add helical propensity to the dimer fold. We were interested to see whether including the MYC-MBIV region c-terminal to the bHLHzip motif would affect DNA affinity and the structural envelope of the MYC-MAX complex. To achieve our aims, we have established the expression and the purification platforms for the Myc and Max proteins. Further, we have developed the biochemical and biophysical (SEC-MALS, ITC, DSF, DLS) characterization of the tertiary complexes, which is a prerequisite for achieving our aims. Jointly, this work has now led to the first description of the extended MYC(MBIV)-MAX-DNA complex using SANS experimental data and computational modeling, which we will present here.

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