A Structure-based Model of the c-Myc/Bin1 Protein Interaction Shows Alternative Splicing of Bin1 and c-Myc Phosphorylation are Key Binding Determinants

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The N terminus of the c-Myc oncoprotein interacts with Bin1, a ubiquitously expressed nucleocytoplasmic protein with features of a tumor suppressor. The c-Myc/Bin1 interaction is dependent on the highly conserved Myc Box 1 (MB1) sequence of c-Myc. The c-Myc/Bin1 interaction has potential regulatory significance as c-Myc-mediated transformation and apoptosis can be modulated by the expression of Bin1. Multiple splicing of the Bin1 transcript results in ubiquitous, tissue-specific and tumor-specific populations of Bin1 proteins in vivo. We report on the structural features of the interaction between c-Myc and Bin1, and describe two mechanisms by which the binding of different Bin1 isoforms to c-Myc may be regulated in cells. Our findings identify a consensus class II SH3-binding motif in c-Myc and the C-terminal SH3 domain of Bin1 as the primary structure determinants of their interaction. We present biochemical and structural evidence that tumor-specific isoforms of Bin1 are precluded from interaction with c-Myc through an intramolecular polyproline–SH3 domain interaction that inhibits the Bin1 SH3 domain from binding to c-Myc. Furthermore, c-Myc/Bin1 interaction can be inhibited by phosphorylation of c-Myc at Ser62, a functionally important residue found within the c-Myc SH3-binding motif. Our data provide a structure-based model of the c-Myc/Bin1 interaction and suggest a mode of regulation that may be important for c-Myc function as a regulator of gene transcription.

Keywords: alternative splicing; NMR structure; oncoprotein; tumor suppressor; intramolecular interaction

Introduction

The cellular myelocytomatosis (c-myc) gene product, c-Myc, belongs to the Myc family of oncoproteins, which are activated in a large number and wide variety of human malignancies.1,2 c-Myc is a nuclear phosphoprotein that functions as a regulator of gene transcription, where its target genes are thought to drive the many biological activities of c-Myc, including transformation, cell-cycle progression, apoptosis and block to differentiation.2,3