Abstract:

Sam68 (Src-associated during mitosis, 68 kDa) is a prototypical member of the STAR (signal transducer and activator of RNA) family of RNA-binding proteins. STAR proteins bind mRNA targets and modulate cellular processes such as cell cycle regulation and tissue development in response to extracellular signals. Sam68 has been shown to modulate alternative splicing of the pre-mRNAs of CD44 and Bcl-xL, which are linked to tumor progression and apoptosis. Sam68 and other STAR proteins recognize bipartite RNA sequences and are thought to function as homodimers. However, the structural and functional roles of the self-association are not known. Here, we present the solution structure of the Sam68 Qua1 homodimerization domain. Each monomer consists of two antiparallel alpha-helices connected by a short loop. The two subunits are arranged perpendicular to each other in an unusual four-helix topology. Mutational analysis of Sam68 in vitro and in a cell-based assay revealed that the Qua1 domain and residues within the dimerization interface are essential for alternative splicing of a CD44 minigene. Together, our results indicate that the Qua1 homodimerization domain is required for regulation of alternative splicing by Sam68.