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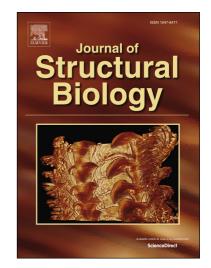
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ACCEPTED MANUSCRIPT

Structure and dynamics of a coiled-coil domain of THAP11

Title:

The C-terminal Region of the Transcriptional Regulator THAP11 Forms a Parallel Coiled-Coil Domain Involved in Protein Dimerization

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Running title: Structure and dynamics of a coiled-coil domain of THAP11

ABSTRACT

Thanatos associated protein 11 (THAP11) is a cell cycle and cell growth regulator differentially expressed in cancer cells. THAP11 belongs to a distinct family of transcription factors recognizing specific DNA sequences via an atypical zinc finger motif and regulating diverse cellular processes. Outside the extensively characterized DNA-binding domain, THAP proteins vary in size and predicted domains, for which structural data are still lacking. We report here the crystal structure of the C-terminal region of human THAP11 protein, providing the first 3D structure of a coiled-coil motif from a THAP family member. We further investigate the stability, dynamics and oligomeric properties of the determined structure combining molecular dynamics simulations and biophysical experiments. Our results show that the C-ter region of THAP11 forms a left-handed parallel homo-dimeric coiled-coil structure possessing several unusual features.

Keywords

THAP11, coiled-coil, oligomerization, crystal structure, NMR, molecular dynamics.

1. Introduction

Thanatos-associated proteins (THAP)¹ form a large family of sequence-specific DNA-binding transcription factors that control a diverse set of eukaryotic cellular processes such as transcriptional regulation, cell proliferation, stem-cell pluripotency, cell cycle progression and transposition (Clouaire et al., 2005; Dejosez et al., 2008; Parker et al., 2012; Roussigne et al., 2003b). THAP proteins have been linked to several severe human diseases such as neurological defects (Fuchs et al., 2009), heart disease (Balakrishnan et al., 2009) and several types of cancer (Lian et al., 2012; Parker et al., 2012). Structurally, the family is defined by the presence of an atypical C2CH zinc finger motif, called THAP domain

¹ The abbreviations used are: THAP, Thanatos-associated protein; HCF-1, host cell factor 1; HBM, HCF-1 binding motif; TEV, tobacco etch virus; LB, Luria-Bertani; IPTG, isopropyl-β-D-1-thiogalactopyranoside; IMAC, immobilized metal affinity chromatography; SEC, size exclusion chromatography; DTT, dithiothreitol; MALS, multiangle light scattering; MD, molecular dynamics; CSI, chemical shift index; hetNOE, 15 N- 1 H heteronuclear NOE; TRACT, TROSY for rotational correlation times; K_d , dissociation constant; RMSD, root-mean-square deviation

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