of APC is the regulation of the level of β-catenin, which is a key Wnt signaling effector. Truncation mutations in APC result in the accumulation of β-catenin in the nucleus, where β-catenin binds to the T cell factor (TCF) and lymphoid enhancer factor, thereby activating the transcription of Wnt target genes.

APC is a multidomain protein that interacts with a variety of proteins. The armadillo repeat (Arm) domain of APC facilitates the interaction of APC with numerous proteins. It was recently found that the Arm domain of APC interacts with the tyrosine-rich (YY) domain of Sam68, the Src-associated in mitosis, 68 kDa protein. It was suggested that the complex between APC and Sam68 negatively regulates TCF-1 alternative splicing, thereby inhibiting Wnt signaling.

In this study, we determined the crystal structures of the APC-Arm fragment, consisting of residues 396–732, and its complex with the Sam68-YY fragment, consisting of residues 365–419. APC-Arm forms a superhelix with a positively charged groove. We mapped the locations of the missense mutations in APC-Arm, identified in familial adenomatous polyposis patients, onto the structure of APC-Arm. The Arg414 and Lys516 residues that are targeted for missense mutations to Cys and Asn residues, respectively, are located on the surface of APC-Arm, and may impair ligand binding.

Sam68-YY adopts a bent conformation, and forms numerous interactions with the residues in the positively charged groove of APC-Arm. To confirm the significance of the crystallographically determined binding sites, we performed isothermal titration calorimetry (ITC) on wild-type APC-Arm and Sam68 mutants, and on APC-Arm mutants and wild-type Sam68. Point mutations were sufficient to abrogate complex formation. To assess whether phosphorylation affects Sam68-YY binding to APC-Arm, we also performed ITC on wild-type APC-Arm and phosphorylated Sam68. Phosphorylation of Sam68 Tyr387, at the apex of the bend, completely abolished binding to APC-Arm.

We compared the structures of the Arm domains of APC and other Arm-containing proteins, such as β-catenin and p120 catenin. We found that while the overall structures of APC-Arm and β-catenin-Arm are similar, their ligand recognition modes differ significantly. On the other hand, both the overall structures and ligand recognition modes are similar between APC-Arm and p120 catenin-Arm. However, the conformations of Sam68-YY and the juxtamembrane domain of E-cadherin, the ligand of p120 catenin-Arm, are different, in that the former is bent while the latter is elongated. We speculate that ligand bending may be a structural determinant for binding to APC-Arm.

Keywords: cancer, complex, crystallography

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Structural insight into the SARAH domain from Mst2 kinase in the apoptosis pathway

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Mst1 and Mst2 (Mammalian Sterile 20-like kinase 1 and 2) are pro-apoptotic protein kinases and involved in cell proliferation and survival. The C-termini of Mst1 and Mst2 contain a common protein-protein interaction domain, named SARAH (Sav/Rassf/Hpo), which is found in three classes of eukaryotic tumour suppressors, Salvador, Rassf, and Hippo. The interaction of these SARAH domains controls apoptosis and cell cycle arrest. Moreover, Mst2 SARAH domain is known to interact with Raf, resulting in the suppression of apoptosis [1]. The SARAH mediated homo- and heterodimerization are crucial in the pathways that induce apoptosis and cell cycle arrest. In this study, we describe the sample preparation and x-ray crystal structure of SARAH domain from Mst2 kinase. The gel-filtration chromatography shows that the SARAH domain of Mst2 forms a homodimer in solution. These results provide a useful information for the structural and functional study of Mst2 SARAH domain in the apoptosis pathway.

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Keywords: mst2 kinase, SARAH domain

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Intermolecular communication between DnaK and GrpE in the DnaK chaperone system

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DnaK is a homolog of the highly conserved ATP-dependent Hsp70 family of chaperone proteins in prokaryotes. The mechanism of peptide association and dissociation in this chaperone protein DnaK is regulated by concerted and consecutive association of co-chaperone proteins DnaJ (Hsp40) and GrpE (nucleotide exchange factor) in the chaperone cycle. Our understanding of detailed mechanism for the interaction among these proteins towards peptide folding remains vague due to insufficient structural information. Here we report the crystal structure of a full-length GrpE homodimer in complex with a functionally intact DnaK chaperone from *Geobacillus kaustophilus HTA426* at 4.1Å resolution. The overall structure represents the nucleotide-free and substrate-bound conformation. The structure demonstrates that the conserved linker region of DnaK is stabilized by the N-terminal long α-helices of the GrpE dimer during ternary complex formation with a hydrophobic peptide. Furthermore we show the possible interaction between substrate-binding domain of DnaK with the N-terminal disordered region of GrpE in accelerating bound substrate release and complex stabilization. These findings provide a molecular mechanism for client substrate binding, processing and release during Hsp70 chaperone cycle.

Keywords: chaperone cycle, heat shock protein 70, protein-protein interaction

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Control of asymmetric cell division in developing *Drosophila* Neuroblasts

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Asymmetric cell division enables small groups of multipotent stem cells to produce a vast range of terminal cells with diverse functions. It plays a key role in the development of higher organisms. In the developing *Drosophila* embryo, the multipotent stem cells, which generate all of the neuronal and glial cells of the adult central nervous system, are known as neuroblasts. Neuroblasts divide asymmetrically along their apico-basal axis to produce a new neuroblast (apical) and a smaller ganglion mother cell (GMC, basal). Whilst the new neuroblast