Sensing actin dynamics: Structural basis for G-actin-sensitive nuclear import of MAL

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1 Introduction

The coordination of cytoskeletal actin dynamics with gene expression reprogramming is emerging as a crucial mechanism to control diverse cellular processes, including cell migration, differentiation and neuronal circuit assembly. The actin-binding transcriptional coactivator MAL (also known as MRTF-A/MKL1/BSAC) senses G-actin concentration and transduces Rho GTPase signals to serum response factor (SRF) [1]. MAL rapidly shuttles between the cytoplasm and the nucleus in unstimulated cells but Rho-induced depletion of G-actin leads to MAL nuclear accumulation and activation of transcription of SRF:MAL-target genes. MAL is implicated in human diseases: MAL was originally discovered as a gene fusion in patients with acute megakaryocytic leukemia, and defective regulation of MAL contributes to cancer cell migration and invasion.

MAL has a multi-domain structure containing an N-terminal actin-binding RPEL domain, a central SRF-binding domain, and a C-terminal transcription activation domain. The N-terminal domain has three tandem repeats (each containing the RPxxxEL sequence motif) in the amino acid sequence. The N-terminal domain is necessary and sufficient for Rho-regulated nuclear accumulation in mouse fibroblast [2]. Herein we report a crystal structure of MAL N-terminal domain in complex with nuclear import receptor (Imp\textsubscript{α}). We also determined a crystal structure of MAL N-terminal domain in complex with five molecules of G-actin. The structures reveal how nuclear import machinery interacts with MAL in a way that responds to changes in G-actin concentrations [3].

2 Experiment

Crystals of MAL-Imp\textsubscript{α} complex and MAL-actin complex were grown by hanging drop vapour diffusion method. X-ray diffraction datasets were collected at Photon Factory and SPring-8 beamlines. The structures of MAL-Imp\textsubscript{α} complex and MAL-actin complex were solved by molecular replacement at a resolution of 2.10 Å and 3.45 Å, respectively.

3 Results and Discussion

The structure of MAL-Imp\textsubscript{α} complex was refined to $R_{\text{free}}$ 20.80 \% ($R_{\text{crys}}$ 16.60\%). The structure shows that MAL has a classical bipartite nuclear localization signal (NLS) in the N-terminal ‘RPEL’ domain (Fig. 1a). The NLS residues of MAL adopt an extended conformation in the amino acid sequence. The N-terminal domain is necessary and sufficient for Rho-regulated nuclear accumulation in mouse fibroblast [2]. Herein we report a crystal structure of MAL N-terminal domain in complex with nuclear import receptor (Imp\textsubscript{α}). We also determined a crystal structure of MAL N-terminal domain in complex with five molecules of G-actin. The structures reveal how nuclear import machinery interacts with MAL in a way that responds to changes in G-actin concentrations [3].

Fig. 1: Overview of the structures of the MAL complexes.
(a) MAL-Imp\textsubscript{α} complex. (b) MAL-actin complex.

References


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