Predicting Actin Interfaces from Genomic Data

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***Short Abstract* — Actin is one of the most abundant proteins found in eukaryotic cells. It plays a crucial role in cell motility, division, and forms the cytoskeleton. The actin filament is a helical polymer and its crystal structure has yet to be solved. Low resolution atomic-models of the filament, constructed using crystallographic data and known G-actin crystal structure, provide useful, but limited, clues as to the interactions involved in filament formation and regulation. Current statistical modeling tools can predict residue pair coevolution from genomic information. Here, we utilize both structural and genomic data to elucidate the functional interactions of actin.**

I. Purpose

Actin is a highly conserved, abundant protein found in every eukaryotic cell where it plays a critical role in cell motility, flexibility, division, and forms the core of the cytoskeleton. It is found in two forms: globular (G) actin, which is unbound and undergoes random diffusion in the cytoplasm, and filamentous (F) actin, which forms when G-actin polymerizes into a long filament. The filament is dynamically regulated by actin-binding proteins (ABPs), which induce viscoelastic changes to the cell. Filament regulation is poorly understood due to a restricted knowledge about its formation, which requires high-resolution structural information. The structure of G-actin was experimentally determined using x-ray crystallography [1]. Conversely, the crystallization of F-actin has remained a significant challenge because actin dimers and trimers are kinetically unstable and rapidly polymerize into filaments [2]. Previous groups have used experimental methods such as x-ray fiber diffraction [3, 4] and cryo-electron microscopy [5] to propose various atomic models of F-actin. While these models have shown that the transition from G- to F-actin is accompanied by a significant structural flattening of G-actin, they are of limited resolution and lack the details needed regarding the functionally relevant DNase I binding loop (D-loop). The D-loop has been implicated in playing a crucial role in the polymerization of actin as well as ensuring filament stability [6]. By determining a high-resolution structure of F-actin and its functional interfaces with ABPs, a great wealth of information regarding how actin functions in cells can be gleaned.

References

[1] Wang, H., et al. Cytoskeleton 67 (2010): 456
[2] Sept, D., et al. Biophysical journal 81 (2001): 667
[3] 3.Holmes, K. C., et al., Nature 347 (1990): 44
[4] 4.Oda, T., et al., Nature 457 (2009): 441
[5] 5.Fujii, T., et al., Nature 467 (2010): 724
[6] 6.Galkin, V. E., et al., Nature structural & molecular biology 17 (2010): 131

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