Multiscale Model of the Formin Homology 1 Domain Illustrates its Role in Regulation of Actin Polymerization

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Actin, indicated in numerous cellular processes, is primarily responsible for cytoskeletal structure. Highly regulated actin polymerization into filaments is key in these processes. Formin, a dimer-forming actin regulator, binds profilin to the polyproline tracks of the proline-rich of its believed flexible Formin Homology (FH) 1 domain. The FH2 domains wrap around the barbed end of the actin filament and elongates the filament processively. Profilin-actin complexes on FH1 domain are modeled to transfer to the barbed end; however, the mechanism is not known. Previous models of the FH1 domain have not captured sequence-specific effects such as the length and distribution of the polyproline tracks and possible variety in mechanosensitivity and response to bound profilin. To remedy this we perform all-atom molecular dynamics simulations of FH1 and show that FH1 is a typical intrinsically disordered protein (IDP), with the polyproline tracks forming high propensity poly-L-proline helices. We develop an alpha-carbon coarse-grained model [1] that retains the sequence-specificity of FH1 domain which is consistent with the IDP notion of FH1, and use this to study the FH1 domain in the context of its biological role. We use the coarse-grained model to investigate the response of FH1 to force and bound profilin.

[1] Y. C. Kim and G. Hummer, J. Mol. Bio. 375, 5. 2008.