How scarce sequence elements control the function of single ß-thymosin/WH2 intrinsically disordered domains in actin assembly

Abstract

Intrinsically Disordered Domains/Regions (IDRs) appear more and more widespread in eukaryotic proteins, especially those implied in regulatory and signaling processes [1]. We will here focus on the case of actin-binding proteins (ABPs), which often exhibit complex multi-domain architectures integrating and coordinating multiple signals and interactions with the dynamic remodeling of actin cytoskeleton [2]. In most modular ABPs, IDRs relay labile interactions with multiple partners and act as interaction hubs in inter-domain and protein–protein interfaces. They thereby control multiple conformational transitions between inactive and active states and play an important role to coordinate the high turnover of interactions in actin self-assembly dynamics. Understanding the functional versatility of IDRs, here in actin assembly, requires deciphering their conformational plasticity and dynamics by multiple structural and functional approaches.
β-thymosin (ßT) and WH2 domains are archetypal intrinsically disordered domains that fold upon binding actin. They display significant sequence variability associated to versatile regulations of actin assembly in motile processes [3]. Here we reveal the structural basis by which, in their basic 1:1 stoichiometric complexes with actin, they either inhibit assembly by sequestering actin monomers (Thymosin-ß4), or enhance motility by directing polarized filament assembly (Ciboulot ßT or WASP/WAVE WH2 domains). Combined mutational, functional, and structural analysis by X-ray crystallography, SAXS and NMR on Thymosin-ß4, Ciboulot and the WH2 domain of WASP-interacting protein (WIP) allowed us to show that functionally different ßT/WH2 domains do not target alternative actin binding sites but rather differ by alternative dynamics of their C-terminal half interactions with G-actin pointed face. We decipher how this interaction dynamics can be controlled by various subtle variations along the whole sequence of these small intrinsically disordered domains. In particular, it depends in specific cases on the presence of a unique ionic interaction in the central part of the sequence [4]. The results open perspectives for elucidating the functions of ßT/WH2 domains in other modular proteins and enlighten how intrinsic structural disorder can lead to a novel mode of functional versatility.

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