Tropomyosin-regulated Actomyosin-based Contractility in Nonmuscle Cells

D.J. Manstein
Hannover Medical School (MHH), Institute for Biophysical Chemistry, Center of Biochemistry, Carl-Neuberg-Str. D-30625 Hannover, Germany

Keywords: *Actin, myosin, tropomyosin, allostery, cooperativity.*

Abstract

Our goal is the elucidation of mechanisms that govern tropomyosin-regulated actomyosin-based contractility in nonmuscle cells. Tropomyosin-binding to bare actin filaments has been described with the notion gestalt-binding. However, gestalt-binding is easily disrupted by other actin-binding proteins and fails to provide a satisfactory explanation for the role of low molecular weight (LMW) isoforms of tropomyosin in the formation of functionally distinct filament populations, which display well-defined isoform-composition and function. Only a minor fraction of actin filaments appears to exist without Tm decoration in mammalian cells. There is growing evidence that decoration of actin filament with LMW-Tm dimers involves a formin-driven co-assembly process. The resulting subpopulations of ATm filaments display differences in localization, pool size, dynamics, organization, and mechanical properties. Kinetic characterization of prototypic ATmM complexes shows how the individual rate and equilibrium constants for nucleotide binding to myosin and myosin binding to actin are modulated in the presence of different actin and cytoplasmic isoforms and how these changes relate to differences in the structural features of isoforms. Structural analysis of ATmM rigor complexes shows how myosin defines and dominates the stereospecific contacts within the ATmM complex. The AM, MTm, and ATm contact areas comprise 1.800, 300, and 210 $Å^2$, respectively. All contact areas involve well-defined electrostatic and hydrophobic interactions. Based on our results, we propose a model where nonmuscle or unconventional myosin isoforms, cytoskeletal actin, and LMW-Tm isoforms are required to establish minimal functional entities with clearly defined properties in cell motility, adhesion, and division. Further analysis of prototypic ATmM complexes with known cellular functions promises to reveal insights in the code that defines structure-function relationships in Tm-regulated actomyosin-based contraction, membrane modelling, and the integration of cellular signaling events.