# New and Notable

## Forcing Filament Fragmentation with Cofilin

Richard B. Dickinson[1,*]
[1]Department of Chemical Engineering, University of Florida, Gainesville, Florida

Numerous cellular processes require the regulated assembly and disassembly of filamentous actin networks. During cell locomotion, for example, actin is assembled into filaments at the plasma membrane to cause lamellipodial or filopodial protrusions. The resulting assembled actin network then translates away from the leading edge by retrograde flow and disassembles at a distance away from the leading edge, thereby freeing actin monomers to continue the treadmilling cycle of assembly and disassembly (1). Understanding the effect of force on actin dynamics in actin-based motility is highly relevant, because actin filaments may be compressed and buckled by polymerization forces at the cell membrane (2). In addition, motor proteins such as myosin work on the sides of actin filaments to compress filament networks and modify network architecture (3). To understand the biophysical basis of actin-based motility, it is therefore essential to understand how polymerization forces and/or motor forces combine to influence actin dynamics.

ADF/Cofilin is a family of proteins among the multitude actin-binding proteins that regulate actin dynamics in order to achieve the precisely controlled actin-network architecture required for various cellular functions. Cofilin 1 (or just cofilin) is a 19-kDa protein that regulates actin dynamics during cell migration by catalyzing actin polymerization and depolymerization by severing actin filaments and increases dendritic nucleation and debranching (4). The extent of cofilin's numerous functions is yet to be determined, but its most studied role has been in promoting filament disassembly. Cofilin binds 1:1 to protomers along the actin filament double helix and does so cooperatively in vertebrate cells; that is, cofilin-bound protomers promote further binding of cofilin adjacent protomers, leading to patches of decorated or bare segments rather than randomly distributed bound subunits along the filament length (5). Filaments decorated with cofilin have altered mechanical properties; bound cofilin makes filaments more flexible, with reduced flexural and torsional rigidities, by loosening the interactions between adjacent actin subunits along the longitudinal helix (6). At the same time, cofilin bridges adjacent subunits to maintain local filament integrity (6). Nevertheless, cofilin binding to actin filaments at low concentrations dramatically promotes net filament disassembly by severing of the filaments and thereby increasing the number of depolymerizing ends. The effect of bound cofilin on filament structure that promotes filament severing is not local; severing is only enhanced close to the boundaries between decorated and undecorated segments, rather than simply uniformly along the cofilin-bound segments (7). This property, together with the cofilin-induced changes to mechanical properties, leads to the fascinating interplay between force and filament severing that is explored by De La Cruz et al. (8) in this issue of the *Biophysical Journal*.

De La Cruz et al. (8) apply Kirchhoff rod theory as a continuum approach to model the elastic deformation of the actin filament under pN-scale compressive forces, while accounting for local modification of the bending and torsional rigidities by bound cofilin molecules. By imposing different patterns of cofilin decoration on compressed, buckled filaments in their simulations, they calculate the effect of cofilin on the distribution of stored mechanical energy, which is assumed to exponentially enhance the local severing probability by pulling the subunit-subunit dissociation reaction toward the activation state. This model makes several interesting predictions about the relationship between force and filament severing, many of which are supported by experimental observations. Consistent with experiments (9), undecorated filaments sever faster than uniformly decorated filaments under the same strain due to a larger amount of stored mechanical energy. However, partially decorated filaments have the highest fragmentation rates; the mechanical heterogeneity along the filament length generated by partial cofilin decoration creates zones of large mechanical energy gradients near the boundaries between decorated and undecorated segments. A small patch of cofilin decoration, which essentially concentrates buckling to a kink in the filament, is predicted to have the highest severing rate. Consequently, force-induced filament severing is highly effective in low cofilin concentrations, consistent with experimental findings (10). Severing becomes more pronounced when buckled filaments are confined laterally, as it would be the case in a dense filament network.

This contribution gives a new insight into the effects of cofilin on filament severing. It points to an important role of force, either due to compression at the leading edge from actin assembly or from myosin motors, in the regulation of actin dynamics, thus providing another important example of the essential coupling of force with biochemical reactions in cytoskeletal dynamics. It also offers a computational framework to address several addition unanswered questions, such as: what effect do long-range propagated effects of cofilin binding

*Submitted March 13, 2015, and accepted for publication April 2, 2015.*

*Correspondence: dickinso@ufl.edu

Editor: David Odde.



0006-3495/15/05/2094/2 $2.00

http://dx.doi.org/10.1016/j.bpj.2015.04.002

cooperativity or on filament structure have on severing? How does mechanical deformation affect cofilin binding? What role do other actin-binding proteins such as tropomyosin play in forced filament fragmentation? Further work based on this computational approach could reveal the answers to these and other important questions in actin biophysics.

## REFERENCES


1. Pollard, T. D., and G. G. Borisy. 2003. Cellular motility driven by assembly and disassembly of actin filaments. *Cell.* 112: 453–465.
2. Dickinson, R. B., L. Caro, and D. L. Purich. 2004. Force generation by cytoskeletal filament end-tracking proteins. *Biophys. J.* 87:2838–2854.
3. Anderson, T. W., A. N. Vaughan, and L. P. Cramer. 2008. Retrograde flow and myosin II activity within the leading cell edge deliver F-actin to the lamella to seed the formation of graded polarity actomyosin II filament bundles in migrating fibroblasts. *Mol. Biol. Cell.* 19:5006–5018.
4. Bravo-Cordero, J. J., M. A. Magalhaes, …, J. Condeelis. 2013. Functions of cofilin in cell locomotion and invasion. *Nat. Rev. Mol. Cell Biol.* 14:405–415.
5. De La Cruz, E. M., and D. Sept. 2010. The kinetics of cooperative cofilin binding reveals two states of the cofilin-actin filament. *Biophys. J.* 98:1893–1901.
6. Fan, J., M. G. Saunders, …, G. A. Voth. 2013. Molecular origins of cofilin-linked changes in actin filament mechanics. *J. Mol. Biol.* 425:1225–1240.
7. Suarez, C., J. Roland, …, L. Blanchoin. 2011. Cofilin tunes the nucleotide state of actin filaments and severs at bare and decorated segment boundaries. *Curr. Biol.* 21:862–868.
8. De La Cruz, E. M., J. -L. Martiel, and L. Blanchoin. 2015. Mechanical heterogeneity favors fragmentation of strained actin filaments. *Biophys. J.* 108:2270–2281.
9. McCullough, B. R., E. E. Grintsevich, …, E. M. De La Cruz. 2011. Cofilin-linked changes in actin filament flexibility promote severing. *Biophys. J.* 101:151–159.
10. Andrianantoandro, E., and T. D. Pollard. 2006. Mechanism of actin filament turnover by severing and nucleation at different concentrations of ADF/cofilin. *Mol. Cell.* 24:13–23.