Adaptive Actin Networks

Julie Plastino[1,2,*] and Laurent Blanchoin[3,4,*]
[1]Institut Curie, PSL Research University, CNRS, UMR 168, 75005 Paris, France
[2]Sorbonne Universités, UPMC Univ Paris 06, CNRS, UMR 168, 75005 Paris, France
[3]CytomorphoLab, Biosciences & Biotechnology Institute of Grenoble, Laboratoire de Physiologie Cellulaire & Végétale, Université Grenoble-Alpes/CEA/CNRS/INRA, 38054 Grenoble, France
[4]CytomorphoLab, Hôpital Saint Louis, Institut Universitaire d'Hematologie, UMRS1160, INSERM/AP-HP/Université Paris Diderot, 75010 Paris, France
*Correspondence: julie.plastino@curie.fr (J.P.), laurent.blanchoin@cea.fr (L.B.)
http://dx.doi.org/10.1016/j.devcel.2017.09.005

Despite their fundamental importance in the regulation of cell physiology, the mechanisms that confer cell adaptability to changes in the microenvironment are poorly understood. A recent study in *Cell* (Mueller et al., 2017) examines the capability of branched actin networks to respond and adapt to mechanical load *in vivo*.

During cell shape changes in general, and cell motility in particular, a dynamic choreography occurs between different actin architectures in different parts of the cell, ensuring a coordinated response of the system as a whole (Blanchoin et al., 2014). Although the main components involved in building the intracellular actin cytoskeleton have been identified and characterized (Blanchoin et al., 2014), a comprehensive description of the mechanisms that define the dynamics and structure of individual actin sub-networks is still lacking. A clear description is important because actin dynamics underlie cells' ability to adapt to external changes.

An example of such a system can be found at the leading edge of the hypermotile epidermal fish keratocyte, where a dense actin network, the lamellipodium, powers cell protrusion. The lamellipodium is built by the Arp2/3 complex, an actin nucleator that initiates branched actin filament growth from the sides of preexisting mother filaments. Lamellipodia turn over on the timescale of minutes, allowing the cell to adjust its locomotion to the microenvironment (Pollard et al., 2000). A high degree of organization of this network is necessary to optimize the relationship between actin assembly and force production (Mogilner and Oster, 1996). Despite the mechanical nature of lamellipodial function, very little was known until recently about the feedback between forces exerted by and against a protruding lamellipodium and actin assembly.

In an elegant experiment *in vitro* using micropatterned surfaces to geometrically control branched actin assembly (Reymann et al., 2010) combined with atomic force microscopy, Bieling and colleagues (Bieling et al., 2016) revealed that a high load exerted against a growing branched actin network increases its density and capability to generate force. As the load is changed from high to low, the actin structure adapts and the overall density of the network decreases. Therefore, cycles between low and high loads generate branched actin networks with different densities, a hallmark of the mechanosensitivity of actin assembly to external force (Bieling et al., 2016). How this material property translates into a cellular context, where the branched actin network is pushing against the plasma membrane and the load is likely provided by membrane tension, is an open question now addressed by Mueller et al. (2017).

Using the lamellipodium of fish keratocytes, Mueller and colleagues (2017) investigated how mechanical perturbation via manipulation of membrane tension affected the lamellipodial response. First, they developed a quantitative analytic approach using a combination of light and electron microscopy to evaluate the structural organization of the lamellipodium and quantify changes induced by variations in membrane tension. To manipulate membrane tension, they employed variable micropipette aspiration of the keratocyte trailing edge. Increasing membrane tension generated a denser actin network in the lamellipodium, consistent with *in vitro* observations (Bieling et al., 2016), together with a change in the orientation of the actin filaments within the network (Figure 1A). Lowering the membrane tension induced a change in the organization of the network and a transition to low actin filament density (Figure 1B). Interestingly, in the lower-density zone, the filaments were oriented perpendicular to the membrane rather than with their typical 35° orientation. To quantitatively explain these observations, the authors developed a stochastic 2D model. The model predicted that decreasing membrane tension increases protrusion velocity with two consequences: a drop in filament density and selective capping by capping proteins of filaments angled away from the membrane, favoring growth of perpendicular actin filaments and thus explaining the change of orientation of actin filaments within the network. This mechanism can be extrapolated to cells in more complex environments, where the load could be a local change in the microenvironment such as an obstacle. This will generate heterogeneity within the lamellipodium that may allow local adaptation of the network to force, modulating the rate and the direction of a protrusion and therefore producing steering during motility (Figure 1C).

It remains to be seen how the results obtained with keratocytes apply to other cell types in which tension sensing appears to have different consequences (Sens and Plastino, 2015). In neutrophils, increases in membrane tension inhibit recruitment of actin assembly factors and protrusion formation at non-leading edge sites, thereby contributing to cell polarity maintenance (Houk et al., 2012).

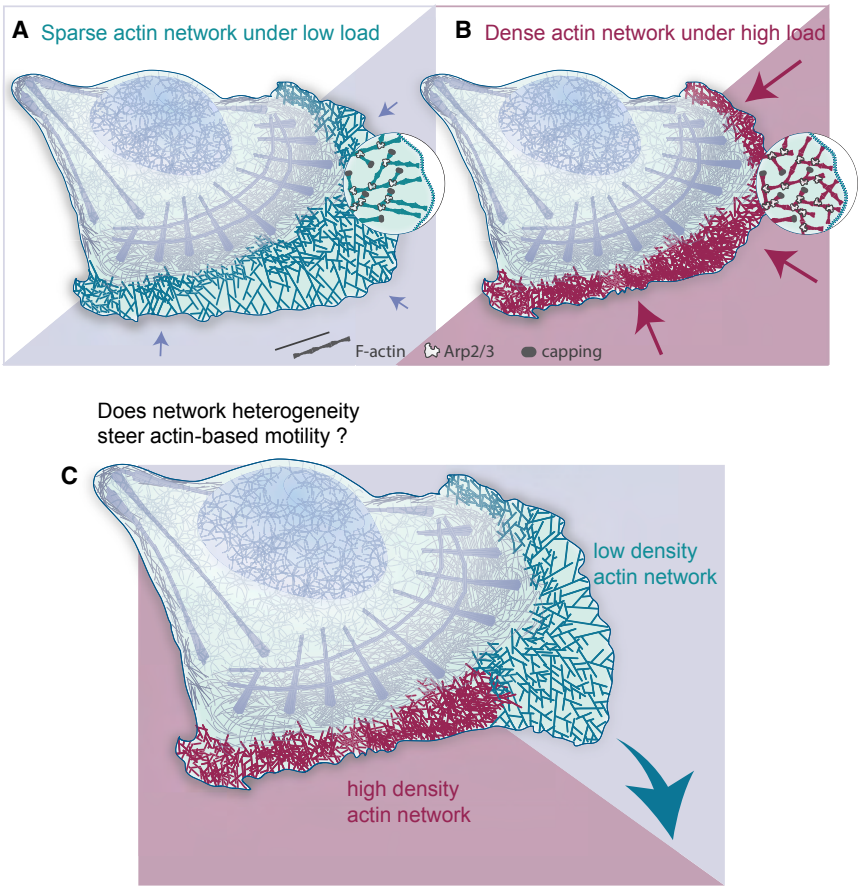

Figure 1. Adaptation of the Lamellipodium to Force
(A) Under low load, the density of the actin network is low, and actin filament orientation is mostly perpendicular to the plasma membrane.
(B) Under high load, the density of the actin network increases, and actin filaments are splayed with respect to the plasma membrane.
(C) Actin network heterogeneity generated by load differentials applied to the lamellipodium could favor steering during motility.

In the *Caenorhabitis elegans* sperm cell, variations in membrane tension regulate the orientation of cytoskeleton filaments inversely to what is observed in the fish keratocyte, i.e., higher tension orients cytoskeletal fibers in the direction of movement (Batchelder et al., 2011). These differences could be due to the involvement of signaling molecules in the mechanical response, which may enable a wide range of adaptive responses depending on cell type and environment. In addition, lamellipodial cytoskeleton binding proteins themselves could be mechanosensitive, as is the case with formins, which modulate the rate of actin filament elongation depending on the load. FMNL formin, for example, is involved in lamellipodia force production (Kage et al., 2017) and may add another level of complexity to the force adaptation of the lamellipodium.

The development of more physiological *in vitro* reconstituted systems, together with progress in cell manipulation and quantitative analysis of dynamic actin changes, will help address these questions and advance our understanding of how dynamic actin organization and function emerge from actin's biochemical, structural, and mechanical properties.

REFERENCES

Batchelder, E.L., Hollopeter, G., Campillo, C., Mezanges, X., Jorgensen, E.M., Nassoy, P., Sens, P., and Plastino, J. (2011). Proc. Natl. Acad. Sci. USA *108*, 11429–11434.

Bieling, P., Li, T.D., Weichsel, J., McGorty, R., Jreij, P., Huang, B., Fletcher, D.A., and Mullins, R.D. (2016). Cell *164*, 115–127.

Blanchoin, L., Boujemaa-Paterski, R., Sykes, C., and Plastino, J. (2014). Physiol. Rev. *94*, 235–263.

Houk, A.R., Jilkine, A., Mejean, C.O., Boltyanskiy, R., Dufresne, E.R., Angenent, S.B., Altschuler, S.J., Wu, L.F., and Weiner, O.D. (2012). Cell *148*, 175–188.

Kage, F., Winterhoff, M., Dimchev, V., Mueller, J., Thalheim, T., Freise, A., Brühmann, S., Kollasser, J., Block, J., Dimchev, G., et al. (2017). Nat. Commun. *8*, 14832.

Mogilner, A., and Oster, G. (1996). Biophys. J. *71*, 3030–3045.

Mueller, J., Szep, G., Nemethova, M., de Vries, I., Lieber, A.D., Winkler, C., Kruse, K., Small, J.V., Schmeiser, C., Keren, K., et al. (2017). Cell *171*, 188–200.

Pollard, T.D., Blanchoin, L., and Mullins, R.D. (2000). Annu. Rev. Biophys. *29*, 545–576.

Reymann, A.-C., Martiel, J.-L., Cambier, T., Blanchoin, L., Boujemaa-Paterski, R., and Théry, M. (2010). Nat. Mater. *9*, 827–832.

Sens, P., and Plastino, J. (2015). J. Phys. Condens. Matter *27*, 273103.