Actin Waves: Origin of Cell Polarization and Migration?

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Keywords: reaction-diffusion, self-organization, clutch molecule, protein translocation, symmetry breaking

Abstract

Actin filaments and associated proteins undergo wave-like movement in various cell types. Recent studies with cutting-edge analyses, including live-cell imaging, biophysical monitoring and manipulation, and mathematical modeling, have highlighted roles of “actin waves” in cellular protrusion, polarization and migration. The prevailing models to explain the wave-like dynamics of actin filaments involve an activator-inhibitor mechanism. In addition, axonal actin waves migrate by means of directional assembly and disassembly of membrane-anchored actin filaments, and thus represent a new type of machinery that translocates their component molecules to the cell edge. Here, we review recent advances in our understanding of the generation, mobility and functions of actin waves, and discuss how actin waves may self-organize into the molecular machinery underlying cell morphogenesis.
Emergence of Actin Waves

Through their dynamic assembly and disassembly, actin and associated proteins play central roles in the regulation of cell shape, enabling cells to protrude, polarize and move. Two decades ago, Vicker and colleagues observed spiral localization patterns of actin filaments in formalin-fixed *Dictyostelium discoideum* cells, and proposed that waves of actin filaments propagate within cells [1]. Shortly after this report, using time-lapse microscopy, movement of wave-like membrane protrusions containing actin filaments was reported in cultured neurons by Ruthel and Banker [2, 3], and then propagation of actin waves in *Dictyostelium* cells was confirmed [4-7]. Although these actin waves did not initially attract much attention, a growing number of studies have shown that actin filaments and related proteins undergo wave-like movement in various types of cells, including neurons [8, 9], *Dictyostelium* cells [10, 11], leukocytes [12, 13], fibroblasts [5, 14], melanoma cells [5, 15], osteosarcoma cells [15], keratocytes [16], oocytes [17] and embryos [17], suggesting that their movement is a ubiquitous phenomenon.

At present, it is unclear whether all these wave-like movements observed in a wide range of cells are driven by a similar molecular mechanism [18]. The term “waves” [2, 4] does not mean that they move by the mechanism of water wave propagation. The prevailing models to explain the actin wave generation involve an excitable activator-inhibitor mechanism, a biochemical process in principle, driven by positive and negative feedback interactions, as discussed in recent reviews [18-20]. On the other hand, a recent study reported a physical mechanism by which directional assembly and disassembly of membrane-anchored actin filaments in waves leads to the translocation of actin filaments and associated proteins [21]. Importantly, accumulating evidence suggests that actin waves are associated with intracellular protein transport [9, 21] as well as cell protrusion [3, 12, 21], polarization [22-24] and migration [10, 24]. In this review, we describe recent progress in our understanding of the mobility mechanisms and functions of actin waves, and discuss how actin and associated proteins are spatiotemporally organized into the molecular machinery for cell protrusion, polarization and migration.

Actin Waves in Various Cell Types

In 1998, Ruthel and Banker reported movement of wave-like membrane protrusions containing actin filaments along the axons and immature neurites of cultured rat hippocampal neurons [2]. These neurites provide an excellent model system to analyze actin waves because of their simple and long one-dimensional morphology. The waves
can be easily identified along the neurite shaft, as they exhibit a fin-like lamellar shape on both sides of the shaft, forming lamellipodia and filopodia as in the case of the axonal leading edge, the growth cone (Figure 1A) [2, 21]. In addition, the thin lamellar shape of the waves is particularly suitable for high-resolution live imaging of actin organization and dynamics (Figure 2A) [21]. Actin waves in neurons are observed preferentially during neuronal polarization and are dependent on actin polymerization [2, 8]. They emerge repeatedly along extending axons and immature neurites, and migrate preferentially toward the tip at an average rate of 3 μm/min (Figure 1A) [2, 8, 25]. Axonal actin waves are enriched with actin filaments and actin-related molecules, such as cortactin, shootin1, GAP-43, ezrin, coflin, LIM-kinase, Slingshot, phosphatidylinositol (3,4,5)-trisphosphate (PIP3), Arp2/3, Cdc42, Rap1, Rac1 and doublecortin (DCX) (Table 1) [8, 9, 21, 22, 25-27]. Importantly, actin waves are also observed in neuronal axons in tissues of the hippocampus and cerebral cortex [9, 21].

Confocal microscopy and total internal reflection fluorescence (TIRF) microscopy allow for observation of actin waves in various non-neuronal cells (Table 1). Vicker [4, 5] and Gerisch's group [6, 7] reported propagation of actin waves in Dictyostelium cells. On the ventral surface of these cells, waves of actin filaments and actin-associated proteins, such as Arp2/3, coronin, CARMIL and Myosin I, propagate at 2-10 μm/min (Figure 1B) [4-7, 10, 11, 28-32]. In addition, PIP3 co-migrates with actin waves [10, 30]. The waves are spontaneously generated depending on actin polymerization [28]. Actin waves coupled with PIP3-rich bands are also observed in large Dictyostelium cells fused by electronic pulses [33]. Hem-1, a constituent of the SCAR/WAVE complex that regulates Arp2/3 activity, and mammalian actin-binding protein 1 (mAbp1) undergo wave-like propagation on the ventral surface of neutrophils toward the leading edge (Figure 1C) [12, 13]. Macrophages cultured on an IgG-coated glass surface form propagating circular actin waves on their ventral surface [34]. In fibroblasts, actin waves including α-actinin, PIP3 and myosin light chain kinase (MLCK) propagate on the lateral or ventral surface [5, 14, 35-38]. Waves in melanoma cells include actin and Abi1, a component of the WAVE complex, and integrin [5, 15, 39, 40]. Osteosarcoma cells generate ventral actin waves containing Arp2/3, and these waves are followed by integrin and focal adhesion proteins, zyxin, VASP, paxillin, vinculin and talin [15]. Fish keratocytes generate lateral actin waves along the leading edge [16, 41]. Xenopus and starfish oocytes and their embryos generate waves of actin filaments and activated Rho on the cortical surface [17]. Interestingly, fin-like actin waves similar to those along axons were also observed in various non-neuronal cells, including fibroblasts, epithelial cells, glioma cells and endothelial cells, when they were
cultured under a particular three-dimensional condition [24]. When these cells are cultured on a thin fiber, they extend a slender process along the fiber; fin-like actin waves emerge repeatedly along the process and migrate preferentially toward the edge (Figure 1D).

**Mechanisms of Actin Wave Generation and Propagation**

*Activator-Inhibitor Mechanism for Actin Wave Generation and Migration*

Since an early proposal by Vicker and colleagues as a reaction-diffusion system [1, 4], widely used models to explain actin wave generation involve an activator-inhibitor mechanism. A combination of autocatalytic positive feedback and slower negative feedback would confer excitability on cells for actin wave generation; readers are referred to recent reviews for details [18-20]. Weiner et al. constructed a simple activator-inhibitor model to describe the Hem-1 wave on the ventral membrane of neutrophils [12]. In this model, Hem-1 acts as an activator that recruits itself to the membrane and stimulates actin polymerization through activation of WAVE and Arp2/3 complex, while actin filaments act as an inhibitor to remove Hem-1 in a delayed fashion and thus disassemble actin filaments. Their model simulated wave-like propagation of Hem-1 on the membrane [12]. In addition, a number of mathematical models for actin waves have been proposed which incorporate diffusible autocatalytic activators for actin polymerization combined with delayed inhibitory mechanisms [17, 37, 42-46]. Details of the molecular networks constituting the activation and inhibition feedbacks remain unknown [18-20].

Bretschneider et al. examined the three-dimensional dynamics of actin and related proteins, myosin-IB, Arp2/3 complex, CARMIL and coronin, in waves of *Dictyostelium* cells, and presented a model in which actin filaments are located in an upright position against the substrate-bound membrane [28]. They proposed that wave propagation is based on the net actin polymerization at the front and net depolymerization at the back of the waves, where actin subunits polymerize at the membrane and disassemble in the upper region. Myosin-IB attached to the membrane together with Arp2/3 complex and CARMIL promotes actin polymerization, while coronin in the upper region inhibits polymerization.

*Directional Assembly-Disassembly Mechanism for Actin Wave Migration*

Katsuno et al. recently reported another model of actin wave migration which is driven by a mechanical process (Figure 2A) [21]. High-resolution live imaging showed that the actin filaments in axonal actin waves are aligned in parallel to the substrate-bound
membrane and undergo directional polymerization and depolymerization, in which the polymerizing ends are on average oriented toward the neurite tip (Figure 2A). The parallel alignment of actin filaments to the membrane is distinct from their upright alignment in the model of Bretschneider et al. [28]. In addition, the actin filaments are mechanically anchored to the plasma membrane and adhesive substrate through the linker clutch molecules (Box 1) shootin1 and cortactin [47, 48] and the cell adhesion molecule L1-CAM [47]. As actin filaments in the wave are anchored parallel to the membrane, directional polymerization/depolymerization of actin filaments leads to wave migration on the membrane toward the neurite tip, with actin subunits exchanging between actin filament arrays and the monomer pool in the cytoplasm (Figure 2A). The velocity of actin wave migration positively correlates with the actin polymerization rate and the degree of the anchoring of actin filaments to the substrate-attached membrane [21]. In addition, traction force microscopy detected directional forces on the substrate concomitant with wave migration [21].

Regulation of Actin Waves by Signaling

Actin waves emerge and propagate spontaneously within cells. However, recent studies reveal that waves are also regulated by cell signaling, providing clues to understanding the mechanisms of wave generation. PIP3, Rac1, Arp2/3, cofilin and shootin1 accumulate in axonal actin waves [8, 9, 25]. Local production of PIP3 or activation of Rac1 by optogenetics generates actin waves along axons, suggesting that PIP3 and Rac1 activity are sufficient to initiate the waves [25, 49]. In addition, inhibition of Arp2/3 complex or formins decreases the velocity of axonal actin wave migration, while active cofilin or PAK1-mediated shootin1 phosphorylation by netrin-1 stimulation increases migration velocity [21]. Similarly, inhibition of phosphatidylinositol 3-kinase (PI3K) (which synthesizes PIP3), Rac1 or N-WASP inhibits the generation of actin waves in Dictyostelium, osteosarcoma and macrophage cells [10, 15, 34]. Thus, these molecules appear to be involved in spontaneous and external signal-mediated generation and propagation of actin waves. Recently, Khamviwath et al. formulated a mathematical model of actin waves in Dictyostelium cells involving actin dynamics and PI3K signaling pathways, and proposed that a balance between positive feedback of actin assembly, actin disassembly, and limited availability of network components is important for actin wave dynamics [50].

The Axonal Actin Wave as a New Type of Intracellular Transport System

Ruthel and Banker, in their seminal paper, proposed that axonal actin waves transport
actin and associated proteins to the growth cone at the tip of an extending axon [2]. Indeed, substantial concentrations of actin in the wave migrate anterogradely, and their arrival at the growth cone increases actin concentration there (Figure 1A) [21]. The actin-associated proteins shooting1, cortactin, cofilin, Arp2/3, ezrin and Slingshot also co-migrate with actin waves [2, 8, 9, 21]. Using photoconvertible Dendra-actin, Flynn et al. directly demonstrated that the migration of actin waves represents anterograde movement of actin molecules [9]. By a combination of quantitative measurement and mathematical modeling, Katsuno et al. demonstrated that the transport mechanism of actin and actin filament-binding proteins is linked to the directional assembly-disassembly mechanism of wave migration (Figure 2B) [21]. Namely, the arrays of actin filaments in waves migrate toward the neurite tip through directional polymerization and depolymerization (Figure 2A). Actin filament-binding proteins co-migrate with the actin filament array through a cycle of dissociation, directional diffusion and association with the filaments.

Importantly, actin subunits and actin-associated proteins dissociating from the rear of the filaments undergo directional forward movement by passive diffusion from this region toward the polymerizing ends, because their concentrations are locally elevated at the rear due to disassembly and lower at the polymerizing ends due to assembly. This directional diffusion allows for their supply to the polymerizing ends for reutilization of the molecules (Figure 2B) [21]. Although individual actin subunits and actin-associated proteins may shuttle between the reutilizing pool and the other diffusible pool, net amounts of actin and actin-associated proteins that are equivalent to those constituting the actin wave are translocated by the directional diffusion. Recently, Vitriol et al. reported two distinct pools of actin subunits supplied for actin polymerization at the leading edge lamellipodia, one derived from actin disassembly and the other from the cytoplasmic pool [51]. These different pools were selectively used by actin nucleators, formins and Arp2/3, depending on the actin monomer-binding protein thymosin β4. We consider that a local pool of disassembled actin may be preferentially reutilized for polymerization, thereby permitting efficient anterograde movement of the labeled actin molecules [9]. Thus, the directional diffusion driven by assembly-disassembly of the filaments can translocate actin subunits and filament-binding proteins toward the growth cone (Figure 2B).

This mechanism is distinct from those of the widely known protein transport systems that utilize motor proteins such as kinesin and dynein [52, 53] (Figure 2B). It is driven by directional diffusion associated with actin polymerization/depolymerization rather than motor proteins, and the transport velocity is roughly 100 times slower than
that of motor protein-based transport. If we were to compare the actin wave and motor protein-based systems to a railway service, the former would be a local train that crawls on the plasma membrane, while the latter would be an express that runs along the cytoskeleton. The passengers of the actin wave get on and off more frequently than those of the express during the transport (double arrows); however, a steady number of passengers are translocated to their destination (Figure 2B).

Functions of Actin Waves

Actin Waves and Cell Protrusion

What are the functions of actin waves? As described above, the axonal actin wave transports actin and actin-associated proteins that are important for axon outgrowth [2, 9, 21]. Live-cell imaging analyses have revealed that the arrival of actin waves at the growth cone is followed by axonal protrusion and branching [3, 8, 9]. The involvement of actin waves in axon outgrowth was directly demonstrated by micro-manipulation of the adhesion substrate: when an adhesion-free gap of 15 μm width was created under the axonal shaft by laser etching, wave migration was blocked at the gap [21]. This in turn inhibited arrival of actin waves at the growth cone, and disrupted axonal protrusion. The properties of axonal actin waves closely resemble those of the growth cones: both structures bear filopodia and lamellipodia [2, 54, 55], are enriched with actin filaments and actin-associated proteins [2, 8, 9, 48, 55], and produce traction forces on the substrate [21, 56-58]. In addition, waves merge eventually with growth cones after they arrive (Figure 1A) [2, 21] and promote neurite branching (i.e., increase the number of growth cones) and increase the growth cone size [9]. Thus, actin waves appear to play an important role in the formation and/or maintenance of the growth cones. Consistent with the earlier observation of Flynn et al. that newly assembled microtubules containing tyrosine-tubulin are localized in waves [9], Winans et al. recently reported that wave propagation enhances polymerization of microtubules along the axonal shaft [49]. They proposed that wave propagation transiently widens the axonal shaft, thereby promoting microtubule polymerization and kinesin-driven transport for axon outgrowth.

Correlation between wave arrival and cell protrusion has also been reported in various non-neuronal cells. The arrival of actin waves at the edge of Dictyostelium cells is followed by forward expansion of the membrane in the form of a broad lamellipodium (Figure 1B) [5, 10, 28, 59]. Similar correlations between the actin wave and leading edge protrusion occur in neutrophils (Figure 1C) [12] and in cells cultured on a thin fiber [24]. In fibroblasts and keratocytes, lateral membrane protrusions undergo wave-like propagation along the leading edge [16, 35-38]. In relation to these
observations, mathematical models have been built to describe actin wave-mediated membrane protrusion and lateral wave migration [38, 45]. A recent study showed that *Dictyostelium* cells sense the curvature of the adhesion substrate by forming actin filament networks and extending protrusions through free space [32]; formation of these actin filament networks was observed in regions where actin waves migrated. In addition, actin waves are also linked with phagocytosis of *Dictyostelium* cells [60] and macrophages [34].

**Cell Polarization and Migration**

Actin waves are further correlated with cellular polarity formation and migration. Neutrophils polarize in response to external chemical signals such as N-formyl-methionyl-leucyl-phenylalanine (fMLP) [61]. Millius et al. reported that Hem-1 waves were generated in neutrophils in response to local and global fMLP applications [39]. These waves propagated asymmetrically toward the cell edge, and their arrival was followed by membrane protrusion leading to morphological polarity formation, thereby suggesting an involvement of actin waves in neutrophil polarization. In addition, correlations of actin waves with cell polarization and migration, respectively, were observed in *Dictyostelium* cells [10, 30] and cells cultured on a thin fiber [24]. Using quantitative live-cell imaging combined with mathematical modeling, Toriyama et al. reported that actin waves contribute to a positive feedback loop for spontaneous neuronal polarization [22, 23]. A key process is wave-driven anterograde shootin1 transport, which leads to fluctuating shootin1 accumulation at the growth cones. This fluctuating mode of wave-mediated protein transport is distinct from the more continuous protein delivery through a motor protein-based transport system [62, 63] (Figure 2B). Intriguingly, a mathematical model showed that an alteration in the time course of the wave transport from a fluctuating mode to a continuous one impaired neuronal symmetry breaking, thereby underscoring the importance of the wave-like fluctuating transport for neuronal polarization [22].

**How Do Actin Waves Contribute to Cell Protrusion, Polarization and Migration?**

Actin filaments polymerize at the leading edge of motile cells and disassemble proximally; this directional actin polymerization plays an essential role in cell protrusion and migration [54, 64]. How, though, is the molecular machinery involving this directional actin polymerization established? Gerisch et al. found, by monitoring the formation of actin filaments during the recovery from actin depolymerization by latrunculin A, that actin polymerization in *Dictyostelium* cells can occur anywhere on
the cell surface, not only at the cell’s edge [59]. During the recovery process, multiple actin patches first appear within the cell. They then move randomly, undergoing fusion and division, reach the cell’s edge, give rise to actin waves that push the edge, and are finally reorganized into the leading edge containing actin filaments.

We consider that the dynamic translocation of actin assemblies as well as the directionality of actin polymerization at the cell’s leading edge may be explained by the directional assembly-disassembly mechanism of actin wave migration [21], although the scheme is rather over-simplified (Figure 3). Namely, actin filaments (or actin arrays) self-assemble within cells thorough activation and inhibition networks (Figure 4, Key Figure), and undergo polymerization and depolymerization in random orientations (red arrows, Figure 3A). If they become anchored to the substrate-attached membrane via clutch molecules, they will migrate on the membrane toward the polymerizing ends (green arrows, Figure 3B-C); thus, the actin arrays translocated to the cell’s edge by the directional assembly-disassembly mechanism are aligned with their polymerizing ends facing outward (Figure 3D). Actin waves would further translocate laterally along the cell’s edge in a direction depending on their angle of polymerization with respect to the edge (black arrows, Figure 3D), as observed in axons [21]. They then assemble into larger arrays and, through clutch coupling (Box 1), generate forces: coupling between the actin arrays and adhesive substrates by clutch molecules produces traction forces on the substrates and concurrently converts actin polymerization into force that pushes the membrane (blue arrows, Figure 3E). These processes would cooperate with other mechanisms proposed in various cells, such as myosin II-mediated contraction at the rear [65], orientation of actin filament bundles by myosin II [66], actin depolymerization-based force at the rear [66], and long-range inhibition by membrane tension [67], thereby contributing to the establishment of cell polarity. The actin arrays at the leading edge of polarized cells generate force for cell migration by clutch coupling (Figure 3F). In this scheme, actin patches and waves act as precursors of the molecular machinery at the leading edge that induces cell protrusion, polarization and migration. External chemical signals may bias these steps by regulating the clutch coupling or actin polymerization [21].

**Concluding Remarks**

Actin waves provide a potential framework to understand how actin and associated proteins are spatiotemporally organized into the molecular machinery for cell protrusion, polarization and migration (Key Figure). In addition, actin waves along axons serve as a new type of machinery that translocates their component molecules to the cell edge. The
molecular details of the activation and inhibition networks for generation and maintenance of actin waves in various cell types remain an important issue for future studies. It is also currently unclear whether wave migration driven by the directional assembly-disassembly mechanism occurs in non-neuronal cells. We expect that some non-neuronal actin waves may utilize this mechanism because they induce leading edge protrusion, a hallmark of mechanical processes; in such cases, the clutch and cell adhesion molecules that work at the cellular leading edge would also operate under the actin waves. Further detailed analyses of actin dynamics within various waves using high-resolution microscopy, as well as force measurement under waves, mechanical/optogenetic wave manipulations and quantitative mathematical modeling, will enhance our understanding of how actin waves are generated and self-organize into the machinery for cell morphogenesis.
Box 1. Clutch Molecules
Clutch molecules are cytoplasmic linker proteins that mechanically couple actin filaments undergoing polymerization/depolymerization with cell adhesion molecules on the plasma membrane [55, 68, 69]. They are thought to play a key role in axon outgrowth and cell migration. Actin filaments polymerize at the leading edge of motile cells and depolymerize proximally. The actin filament-adhesion coupling by clutch molecules (clutch coupling) produces traction forces on adhesive substrates and concurrently converts actin polymerization into force that pushes the leading edge membrane, thereby promoting axon outgrowth and cell migration. Modulation of clutch coupling is thought to regulate axon guidance and cell migration [57, 68, 69]. In the axonal growth cone and actin wave of hippocampal neurons, shootin1 and cortactin function as clutch molecules that couple actin filaments and the cell adhesion molecule L1-CAM [21, 47, 48]. In addition, multiple proteins including α-catenin, β-catenin, talin and vinculin are thought to function as clutch molecules at the leading edges of neuronal and non-neuronal cells [55, 70-72], and shootin1b, a splicing isoform of shootin1 which is expressed in non-neuronal cells, was recently reported [73].

Acknowledgements
We thank Y. Sakumura and M. Toriyama for critical reading of the manuscript. Our work was supported by a JSPS Grant-in-Aid for Scientific Research on Innovative Areas (25102010, N.I.), JSPS KAKENHI (23370088 and 26290007, N.I.), a JSPS Research Fellowship for Young Scientists (H.K.), the Osaka Medical Research Foundation for Incurable Diseases (H.K. and N.I.) and Takeda Science Foundation (N.I.)

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Figure 1. Wave-like Movement of Actin and Associated Proteins within Various Cell Types.

(A) An actin wave enriched with actin filaments migrating along an axon of a cultured rat hippocampal neuron. Red and green colors indicate mRFP-actin and AcGFP (volume marker), respectively. Arrival of the actin wave (arrowheads) at the growth cone (asterisks) increases actin concentration there. (B) Actin waves propagating in a Dictyostelium cell. Red and green colors indicate mRFP-LimEΔ (marker of actin filaments) and GFP-Arp3, respectively. Arrival of an actin wave (arrowheads) at the cell’s edge correlates with its forward expansion. The numbers indicate seconds. (C) Hem-1 waves in HL-60 neutrophils labeled by Hem-1-YFP. The lower panel shows time courses of wave and leading edge advances. Arrival of the waves (triangle and squares) at the cell’s edge (circles) is followed by leading edge advance (circles). (D) The upper panel shows actin waves in a 3T3 fibroblast cultured on a fiber. Fin-like actin waves (arrowheads) are observed along a slender process. Red color indicates GFP-actin. The lower panel is a kymograph showing propagation of an actin wave (arrow). Scale bars, 10 μm (A and B). Reproduced from [21] (A), [28] (B), [12] (C) and [24] (D).
Figure 2. Directional Assembly-Disassembly Mechanism for Actin Wave Migration and Protein Transport along Axons.

(A) Mechanism for axonal actin wave migration. The upper left panel shows a fluorescent speckle image of mRFP-actin in a wave. A kymograph of the indicated rectangular region at 5-sec intervals is shown to the right. Actin filaments polymerize at the leading edge, accompanied by their retrograde flow (dashed yellow lines). The illustrations describe the molecular mechanism. The actin filaments in axonal actin waves undergo directional polymerization and depolymerization, in which the polymerizing ends are on average oriented toward the neurite tip (top view, lower left), and are anchored to the plasma membrane and substrate through the linker clutch molecules shootin1 and cortactin and the cell adhesion molecule L1-CAM (side view, right). As actin filaments in the wave are anchored in parallel with the membrane, directional polymerization/depolymerization of actin filaments leads to wave migration on the membrane toward the neurite tip. (B) Axonal actin waves as a new type of intracellular transport system. Arrays of actin filaments in a wave migrate through...
directional polymerization and depolymerization (upper panel). Actin filament-binding proteins co-migrate with the actin filament array through cycles of dissociation, directional diffusion, and association with the filaments. The transport velocity is roughly 100 times slower than that of motor protein-based transport (lower panel). Although individual actin subunits and actin-associated proteins may shuttle between the reutilizing pool and the other diffusible pool (double arrows), net amounts of actin and actin-associated proteins that are equivalent to those constituting the actin wave are translocated by the directional diffusion. Scale bar, 5 μm (A). Reproduced from [21] (A).
Figure 3. A Model to Explain How Actin Waves Contribute to Cell Polarization and Migration.

(A) Actin filaments (or actin arrays) self-assemble in random orientations, and undergo polymerization and depolymerization within cells (red arrows). (B and C) If they become anchored to the plasma membrane via clutch molecules, they will migrate on the membrane toward the polymerizing ends (green arrows). (D) The actin arrays translocated to the cell’s edge are aligned polymerizing-end-outward. Actin waves further translocate laterally along the cell’s edge depending on their angle of polymerization with respect to the edge (black arrows). (E) They assemble into larger arrays and generate force that pushes the membrane (blue arrows). (F) The cell polarizes morphologically, and actin arrays at the cell’s leading edge generate force for cell migration (blue arrows).
Figure 4 Key Figure: Self-organization of Actin Waves into the Molecular Machinery for Cell Morphogenesis.

Actin filaments (or actin arrays) self-assemble in random orientations, through activation and inhibition networks (black loops), and undergo polymerization and depolymerization within cells (red arrays). They then migrate toward the cell edge in the form of waves through the activator-inhibitor, the directional assembly-disassembly, or an unknown mechanism (green arrow). The waves assemble into larger arrays and push the membrane (blue arrows). The cell polarizes morphologically, and actin arrays at the cell’s leading edge generate force for cell migration.
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