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Actin Waves: Dynamic F-Actin Networks Guiding Multiple Biological Functions

Introduction

Actin structures in the cellular cortex can create dynamic wave-like patterns that were first observed in the soil amoeba *Dictyostelium discoideum* nearly 30 years ago.[1,2] Actin waves have since been found in many other cell types including neutrophils, dendritic cells, T cells, neurons, endothelial cells, fibroblasts, and keratocytes.[1,3,4]

While actin waves differ considerably in their morphology, propagation speed, and biochemical composition[3] (Figure 1), they can be broadly defined as "micron-scale cytoskeletal regions of increased filamentous actin density that propagate in a wave-like fashion in the actin cortex".[1] Much early work investigated their role in cell migration and division,[1] but a far wider range of functional roles is now emerging. In this newsletter, we will review how our understanding of actin waves has developed since their initial discovery and highlight important recent findings suggesting vital biological roles on a multicellular scale.

Spontaneous Generation of Actin Waves

One key early question concerned the origin of actin waves. By applying theoretical principles from other wave phenomena, it was demonstrated that the cellular actomyosin cortex displays the properties of an excitable medium.[5–7] These systems are capable of spontaneous wave generation, and in the case of the cellular cortex, tuning of the system (i.e., the activation threshold) depends on the balance between the spatiotemporal distribution of actin nucleators and the rate of F-actin assembly. Above a certain threshold of local nucleator concentration, a wave will be initiated.[8] Negative feedback between F-actin and actin nucleators[7,9] completes the activator–inhibitor dynamics typical of excitable systems. Therefore, the ability to generate and propagate actin waves is an inherent characteristic of the actomyosin cortex as an "active adaptive material".[10]

Actin Waves Guide Cellular Movement

In an adaptive excitable medium, external perturbations can provoke wave formation. An important early discovery was force-induced rearward actin waves in lamellipodia, which transport an α-actinin and MYLK signaling complex from the tip to the base of the lamellipodium to control contraction/extension cycles.[11] Other research investigated actin waves generated by the WAVE regulatory complex in neutrophil-like HL-60 cells.[12] Experimental observations were consistent with the model of autoactivation and delayed inhibition (due to slow diffusion of F-actin) developed in theoretical studies, and the authors suggested that cell motility in chemotaxis relies on the collective action of multiple actin waves.

More generally, it was proposed that spontaneous actin wave dynamics can explain amoeboid-like cellular random walks.[6,7] This was elegantly demonstrated in dendritic cells,[9] which exhibit random walk behavior as they patrol tissues in search of pathogens. Dendritic cell trajectories were mapped and could be modeled based on intrinsic actin wave dynamics, illustrating how these cells can adaptively control their migration patterns by regulating actin nucleator distribution and actin polymerization rates. The Arp2/3 complex and Ena/VASP actin nucleators are known to be important for normal dendritic cell motility.[9,13]

Other Excitable Networks Tune Actin Dynamics

Study of actin waves has also revealed pulsatile behavior of related signaling molecules that exhibit excitable dynamics.[10,14] For example, in oocytes and embryonic cells undergoing cytokinesis, waves of Rho activity propagate immediately ahead of actin waves.[15] Small GTPases such as RhoA can act as excitable fast-diffusing activators due to autocatalytic propagation of their active forms.[16] Analogously to actin waves, delayed negative feedback comes from F-actin mediated inhibition of Rho activity at the rear of the wave, leading to the observed traveling wave patterns.[15] Thus, the activation–inhibition characteristics of an excitable medium are also evident with Rho activity.

A related mechanism is seen in *C. elegans* embryos, where delayed negative feedback comes from two Rho GAPs (RGA-3/4) that are recruited by F-actin to extinguish small GTPase activity at the rearward side of the leading Rho waves.[10,17] Other results have shown further fine-tuning of actin wave dynamics by Ras activity, with relatively small variations proving sufficient to elicit profound changes in wave size, speed, and firing rate.[18]

These findings illustrate the emerging concept of a distinct signal-transduction excitable network (STEN) that senses chemical cues, paralleling to the sensing of physical cues by the cytoskeletal excitable network (CEN) that relies solely on the intrinsic properties of the actomyosin cortex as an excitable medium.[14]

In cells contacting collagen-mimicking nanoridges, STEN- and

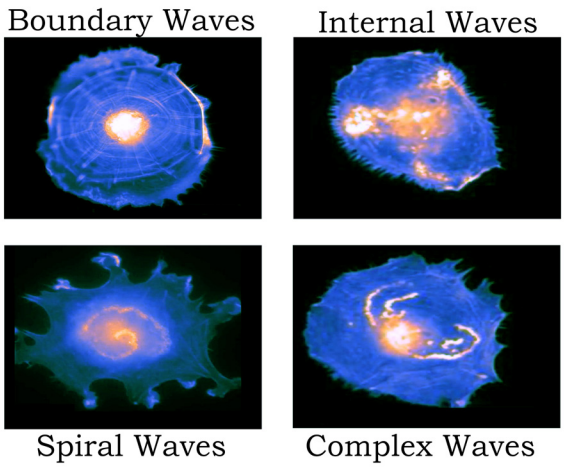

Figure 1. Schematic representation of different actin wave types observed in cultured human aortic endothelial cells (adapted from Riedl M. et al Nat Commun. 2023; ref. 4).

Continued from Page 1

CEN-derived waves were confined to different areas, with CEN waves more likely to be initiated directly along the ridges.[19] Thus, crosstalk between the STEN and CEN excitable systems is assumed to be essential in integrating different environmental cues to properly direct cellular migration.

Emerging Functions of Actin Waves

In support of the above view, it has been established that the CEN and STEN systems can both sense electric fields. Notably, skin wounds rapidly elicit strong bioelectric fields that provide important cellular guidance cues during wound repair[20] and gradually weaken as healing progresses.[21] Electrotaxis, or directed migration of cells in electric fields, is an important phenomenon in regeneration and development as well as wound healing.[22]

In giant *D. discoideum* cells, electric fields were seen to polarize actin wave nucleation and guide wave propagation, thereby mediating electrotaxis.[22] While these fields guided actin waves globally, even when the field direction was switched, nanoridges still induced localized actin waves (via the CEN system) that followed the ridges, implying that local and global tuning of excitable systems both function in complementary fashion to interpret multiple guidance cues through changes in actin dynamics.[23]

Intriguingly, the properties of actin filaments as "biological electrical wires" were recognized 30 years ago,[24] and it is established that actin filaments orient themselves to align with electric fields.[25] Since endogenous bioelectric networks are emerging as an autonomous layer of patterning control in development and regeneration,[26] it seems possible that bioelectrically guided actin waves may underlie cellular organization during morphogenesis, including wound repair, in response to the electrical cues that govern biological pattern formation.

On a different note, it is well known that cancer cells upregulate glycolysis even under normoxic conditions (referred to as the Warburg effect). New results have revealed that glycolytic enzymes are recruited to the cellular cortex and colocalize with actin waves.[27] This suggests that cancer cells rely on direct energy production in the cortex to drive migration, exploiting rapid[28] and localized ATP production through glycolysis. While previous studies have implicated glycolysis as an energy source for cancer cell motility,[29,30] its functional association with actin waves offers new mechanistic insight into the Warburg effect. Relative to nontransformed cells, cancer cells showed higher glycolysis and actin wave activities that progressively increased with metastatic index.[27]

New Developments and Outlook

Exciting recent work has uncovered synchronization of actin waves in cellular ensembles and collective motion.[4] Consistent with observations in other cell types, the nucleation frequency of actin waves was correlated with migration speed in human aortic endothelial cells, but isolated cells moved differently when at low density. At confluency, coherent collective motion was observed that could be associated with synchronization of actin wave nucleation frequencies. The authors referred to this as "frequency locking" to enable ordered collective motion. Deducing the associated coupling mechanisms will be a fascinating avenue of future research, as will other efforts to build our understanding of actin waves beyond the cellular level and interpret them in terms of biological function on the scale of tissues and organs.

Unlabeled Actin Proteins

Unlabeled Actins	Amount	Cat . #
Actin Protein Rabbit skeletal muscle	4 x 250 µg 2 x 1 mg 5 x 1 mg 10 x 1 mg	AKL99-A AKL99-B AKL99-C AKL99-D
Actin Protein Rabbit skeletal muscle	1 x 1 mg 5 x 1 mg	AKL95-B AKL95-C
Actin Protein Bovine cardiac muscle	1 x 1 mg 5 x 1 mg	AD99-A AD99-B
Actin Protein Smooth muscle, chicken gizzard	1 x 1 mg 5 x 1 mg	AS99-A AS99-B
Actin Protein Human platelet, non-muscle	2 x 250 µg 1 x 1 mg	APHL99-A APHL99-C
Pre-formed Actin Filaments Rabbit skeletal muscle	1 x 1 mg 5 x 1 mg	AKF99-A AKF99-B

References

1. Beta C, Edelstein-Keshet L, Gov N, Yochelis A. From actin waves to mechanism and back: How theory aids biological understanding. Elife. 2023;12:e87181. https://doi.org/10.7554/eLife.87181.

2. Vicker MG, Xiang W, Plath PJ, Wosniok W. Pseudopodium extension and amoeboid locomotion in Dictyostelium discoideum: Possible autowave behaviour of F-actin. Physica D. 1997;101(3–4):317–332. https://doi.org/10.1016/S0167-2789(96)00224-2.

3. Beta C, Gov NS, Yochelis A. Why a large-scale mode can be essential for understanding intracellular actin waves. Cells. 2020;9(6):1533. https://doi.org/10.3390/cells9061533.

4. Riedl M, Mayer I, Merrin J, Sixt M, Hof B. Synchronization in collectively moving inanimate and living active matter. Nat Commun. 2023;14(1):5633. https://doi.org/10.1038/s41467-023-41432-1.

5. Doubrovinski K, Kruse K. Cytoskeletal waves in the absence of molecular motors. Europhys Lett. 2008;83(1):18003. https://doi.org/10.1209/0295-5075/83/18003.

6. Doubrovinski K, Kruse K. Cell motility resulting from spontaneous polymerization waves. Phys Rev Lett. 2011;107(25):258103. https://doi.org/10.1103/PhysRevLett.107.258103.

7. Ecker N, Kruse K. Excitable actin dynamics and amoeboid cell migration. PLoS One. 2021;16(2):e0246311. https://doi.org/10.1371/journal.pone.0246311.

8. Motoike IN, Adamatzky A. Three-valued logic gates in reaction–diffusion excitable media. Chaos Solitons Fractals. 2005;24(1):107–114. https://doi.org/10.1016/j.chaos.2004.07.021.

9. Stankevicins L, Ecker N, Terriac E, et al. Deterministic actin waves as generators of cell polarization cues. Proc Natl Acad Sci U S A. 2020;117(2):826–835. https://doi.org/10.1073/pnas.1907845117.

10. Staddon MF, Munro EM, Banerjee S. Pulsatile contractions and pattern formation in excitable actomyosin cortex. PLoS Comput Biol. 2022;18(3):e1009981. https://doi.org/10.1371/journal.pcbi.1009981.

11. Giannone G, Dubin-Thaler BJ, Döbereiner H-G, Kieffer N, Bresnick AR, Sheetz MP. Periodic lamellipodial contractions correlate with rearward actin waves. Cell. 2004;116(3):431–443. https://doi.org/10.1016/s0092-8674(04)00058-3.

12. Weiner OD, Marganski WA, Wu LF, Altschuler SJ, Kirschner MW. An actin-based wave generator organizes cell motility. PLoS Biol. 2007;5(9):e221. https://doi.org/10.1371/journal.pbio.0050221.

13. Visweshwaran SP, Nayab H, Hoffmann L, Gil M, Liu F, Kühne R, Maritzen T. Ena/VASP proteins at the crossroads of actin nucleation pathways in dendritic cell migration. Front Cell Dev Biol. 2022;10:1008898. https://doi.org/10.3389/fcell.2022.1008898

14. Miao Y, Bhattacharya S, Banerjee T, et al. Wave patterns organize cellular protrusions and control cortical dynamics. Mol Syst Biol. 2019;15(3):e8585. https://doi.org/10.15252/msb.20188585.

15. Bement WM, Leda M, Moe AM, et al. Activator–inhibitor coupling between Rho signalling and actin assembly makes the cell cortex an excitable medium. Nat Cell Biol. 2015;17(11):1471–1483. https://doi.org/10.1038/ncb3251.

16. Tsyganov MA, Kolch W, Kholodenko BN. The topology design principles that determine the spatiotemporal dynamics of G-protein cascades. Mol Biosyst. 2012;8(3):730–743. https://doi.org/10.1039/c2mb05375f.

17. Michaux JB, Robin FB, McFadden WM, Munro EM. Excitable RhoA dynamics drive pulsed contractions in the early C. elegans embryo. J Cell Biol. 2018;217(12):4230–4252. https://doi.org/10.1083/jcb.201806161.

18. Lin Y, Pal DS, Banerjee P, et al. Ras-mediated homeostatic control of front–back signaling dictates cell polarity. bioRxiv. Preprint posted online September 1, 2023. https://doi.org/10.1101/2023.08.30.555648.

19. Yang Q, Miao Y, Banerjee P, et al. Nanotopography modulates intracellular excitable systems through cytoskeleton actuation. Proc Natl Acad Sci U S A. 2023;120(19):e2218906120. https://doi.org/10.1073/pnas.2218906120.

20. Tai G, Tai M, Zhao M. Electrically stimulated cell migration and its contribution to wound healing. Burns Trauma. 2018;6:20. https://doi.org/10.1186/s41038-018-0123-2

21. Nuccitelli R, Nuccitelli P, Ramlatchan S, Sanger R, Smith PJS. Imaging the electric field associated with mouse and human skin wounds. Wound Repair Regen. 2008;16(3):432–441. https://doi.org/10.1111/j.1524-475x.2008.00389.x.

22. Yang Q, Miao Y, Campanello LJ, et al. Cortical waves mediate the cellular response to electric fields. Elife. 2022;11:e73198. https://doi.org/10.7554/eLife.73198.

23. Bull AL, Campanello L, Hourwitz MJ, Yang Q, Zhao M, Fourkas JT, Losert W. Actin dynamics as a multiscale integrator of cellular guidance cues. Front Cell Dev Biol. 2022;10:873567. https://doi.org/10.3389/fcell.2022.873567.

24. Lin EC, Cantiello HF. A novel method to study the electrodynamic behavior of actin filaments. Evidence for cable-like properties of actin. Biophys J. 1993;65(4):1371–1378. https://doi.org/10.1016/S0006-3495(93)81188-3.

25. Arsenault ME, Zhao H, Purohit PK, Goldman YE, Bau HH. Confinement and manipulation of actin filaments by electric fields. Biophys J. 2007;93(8):L42–L44. https://doi.org/10.1529/biophysj.107.114538.

26. Levin M. Endogenous bioelectrical networks store non-genetic patterning information during development and regeneration. J Physiol. 2014;592(11):2295–2305. https://doi.org/10.1113/jphysiol.2014.271940.

27. Zhan HD, Borleis J, Janetopoulos C, Devreotes P. Abstract 288: Glycolysis is enriched to propagating waves in cell cortex as a new mechanism for cancer progression. Cancer Res. 2023;83(7_Suppl):288. https://doi.org/10.1158/1538-7445.am2023-288.

28. Zheng J. Energy metabolism of cancer: Glycolysis versus oxidative phosphorylation. Oncol Lett. 2012;4(6):1151–1157. https://doi.org/10.3892/ol.2012.928.

29. Shiraishi T, Verdone JE, Huang J, et al. Glycolysis is the primary bioenergetic pathway for cell motility and cytoskeletal remodeling in human prostate and breast cancer cells. Oncotarget. 2015;6(1):130–143. https://doi.org/10.18632/oncotarget.2766.

30. Zanotelli MR, Zhang J, Reinhart-King CA. Mechanoresponsive metabolism in cancer cell migration and metastasis. Cell Metab. 2021;33(7):1307–1321. https://doi.org/10.1016/j.cmet.2021.04.002.

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G-Actin/F-actin In Vivo Assay Biochem Kit Measure the distribution of monomer and polymer actin	30-100	BK037