attachment (attachment of sister kinetochores to opposite spindle poles) and, presumably, microtubule stabilization. Probably due to the multipolar nature of the centrosome-free meiotic spindle in mouse oocytes even when kinetochores become active players, biorientation is not achieved easily. By monitoring distances between centromeres in paired homologs during the late phases of alignment in meiosis I, Kitajima and Ellenberg (Kitajima et al., 2011) provided an impressive quantitative overview of chromosomes' multiple attempts to biorient and demonstrated that Aurora B kinase is crucial for the correction of the many erroneous attachments.

A very intriguing implication from these studies is that chromosomes might exercise temporal control on the ability of their kinetochores to form end-on attachments, as also hypothesized in a previous study (Gassmann et al., 2008). It is possible that the suppression of sturdy end-on attachment in early mitosis serves the purpose of preventing the formation of tight kinetochore-microtubule interactions before spindle bipolarization, which has been shown to enhance the risk of chromosome attachment errors and lagging chromosomes at anaphase (Ganem et al., 2009).

The ability to observe unperturbed chromosome movements in live dividing cells at the impressive resolution obtained in these studies is bound to lead the way to more quantitative analyses of mitotic and meiotic perturbations. Such perturbations are believed to be at the heart of what is probably the most frequent, and paradoxically most often ignored, genetic abnormality of cancer cells, aneuploidy. As importantly, in oocytes aneuploidies generated in the first meiotic division are the leading cause of infertility and severe congenital diseases. Accurate descriptions of the proceedings of cell division will shed a new light on mitosis under normal and pathological conditions.

REFERENCES

Ganem, N.J., Godinho, S.A., and Pellman, D. (2009). Nature *460*, 278–282.

Gassmann, R., Essex, A., Hu, J.S., Maddox, P.S., Motegi, F., Sugimoto, A., O'Rourke, S.M., Bowerman, B., McLeod, I., Yates, J.R., 3rd., et al. (2008). Genes Dev. *22*, 2385–2399.

Kapoor, T.M., Lampson, M.A., Hergert, P., Cameron, L., Cimini, D., Salmon, E.D., McEwen, B.F., and Khodjakov, A. (2006). Science *311*, 388–391.

Kirschner, M., and Mitchison, T. (1986). Cell *45*, 329–342.

Kitajima, T.S., Ohsugi, M., and Ellenberg, J. (2011). Cell *146*, this issue, 568–581.

Magidson, V., O'Connell, C.B., Lončarek, J., Paul, R., Mogilner, A., and Khodjakov, A. (2011). Cell *146*, this issue, 555–567.

Mitchison, T., and Kirschner, M. (1984). Nature *312*, 237–242.

Mitchison, T.J., and Kirschner, M.W. (1985). J. Cell Biol. *101*, 766–777.

Tanaka, T.U. (2010). EMBO J. *29*, 4070–4082.

Wollman, R., Cytrynbaum, E.N., Jones, J.T., Meyer, T., Scholey, J.M., and Mogilner, A. (2005). Curr. Biol. *15*, 828–832.

Elongated Membrane Zones Boost Interactions of Diffusing Proteins

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Biological membranes are two dimensional, making the discovery of quasi-one-dimensional diffusion of membrane proteins puzzling. Jaqaman et al. (2011) now show that actomyosin and tubulin interact to establish long, thin diffusion corridors, thereby increasing the effective concentration of select membrane proteins to promote their interactions and modulate signaling.

Ever since Gorter and Grendel's discovery 80 years ago that red blood cells have enough lipid for two molecular layers, biologists have been debating how proteins diffuse and interact in the membrane bilayer. A more recent part of the debate, the lipid raft model, rejects the notion that membrane proteins are homogenously distributed in favor of a model in which membrane proteins are characterized as raft-associated or not (Lingwood and Simons, 2010). This generalization, however, has proven a simplification, and other models for limiting receptor diffusion have since been proposed. Observed confinement zones have led to "fence" models (Morone et al., 2006). In this issue, Jaqaman et al. (Jaqaman et al., 2011) consolidate the general idea of "fence" models and extend the paradigm by showing that the integral membrane protein CD36 clusters in elongated Brownian trajectories, effectively increasing protein concentration.

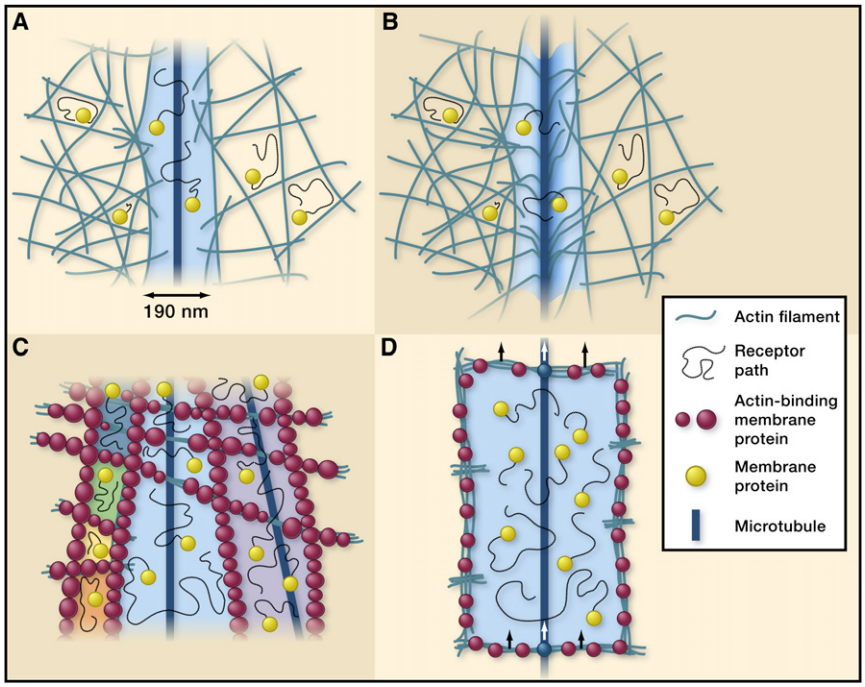

Figure 1. Four Models of Microtubule-Dependent Modulation of Membrane Protein Diffusion

(A) In model 1, adapted from Jaqaman et al. (2011), tubulin causes local disruption of cortical actin.
(B) In model 2, adapted from Jaqaman et al. (2011), tubulin acts to separate cortical actin spatially from the bilayer, disrupting actin-membrane interactions and leading to altered diffusion of membrane proteins.
(C) Tubulin displaces actin-binding membrane proteins (ABMPs) to open paths for membrane protein diffusion along elongated linear corrals.
(D) Tubulin-dependent motor proteins anchored by ABMPs to actin corrals mediate corral translation.

Their findings suggest that these one-dimensional confinement zones influence rates of receptor collision and modulate signaling.

One-dimensional movement within the two-dimensional membrane has been observed previously in studies of hemagglutinin diffusion on fibroblasts (Hess et al., 2007). Now, Jaqaman et al. show that the diffusion of CD36 on macrophages is likewise mostly in one dimension. However, within these one-dimensional domains, receptor movement is isotropic without directional bias on millisecond timescales (Figure 1). Instead, the confinement reduces the dimensionality of diffusion and the area in which CD36 can move, such that the effective concentration is increased. In other words, when degrees of freedom are restricted from two dimensions to one, the area of interaction grows as the perimeter of the domain grows, at constant area. Analytically, the effect of dimensionality on the kinetics of diffusion-controlled reactions was solved by considering the trajectory of a diffusing particle at limiting small step sizes, modeled as a Wiener trajectory, with a thickness determined by the critical collisional radius of the interacting particles (Berezhkovskii et al., 1989). When the diameter of the diffusing particle is on the order of the width of the domain, then that thickened trajectory—a Wiener sausage—has an increased area of interaction (Berezhkovskii et al., 1989). This has important implications for protein-protein interactions, particularly by promoting weak interactions. Consistent with predictions by this model, Jaqaman et al. show that the increased effective concentration leads to increased cell signaling of CD36.

The geometry of the confinement domains itself can mediate gradients in protein concentration even without protein-protein interactions. This is supported by the idea that, for a mobile membrane component with an average diffusion rate of D~0.1 $\mu m^2/s$, the observed confinement zone width allows diffusion in the narrow dimension such that concentration gradients can be dissipated on timescales of ~180 ms. For a length of ~1 μm, the end-to-end motion would average ~28 times longer, allowing transient concentration gradients on timescales of a few seconds. For D~0.01 $\mu m^2/s$, the lengthwise timescale would approach tens of seconds. Thus, an elongated domain promotes protein concentration gradients. The observation by Jaqaman et al. that CD36 concentration increases near the domain perimeter and the increased diffusion coefficient of CD36 within the linear confinement zones may also help to explain the measured increase in collision rate.

Data from Jaqaman et al. and previous studies suggest a potentially general model for membrane heterogeneity through cytoskeletal interactions. For instance, the confinement dimension for CD36 matches that reported for H-Ras (Semrau and Schmidt, 2007). Also, their findings are largely consistent with the picket fence model proposed by Kusumi and colleagues allowing for small modifications. Building on Goswami et al. (2008), Jaqaman et al. show how cortical actin and actomyosin control membrane organization. The convergence of data invoking a cortical cytoskeletal layer suggests a model in which numerous interacting protein partners as well as lipid interactions create these confinement zones (Morone et al., 2006).

Actin and tubulin working together to organize the membrane (e.g., tubulin-dependent redistribution of cortical actin) enable significantly greater specificity and variety of function to be orchestrated by membrane-cytoskeleton interactions. Essentially, more subtle patterns of membrane localization and a variety of dynamic processes are unlocked. Most importantly, this cooperativity provides a second channel of communication between the internal system of cytoskeleton radiating from the centrosomes (microtubules) and the cortical layer of actin—a diffusive channel to complement the motor-driven active channel on the microtubule. For cells in tissues with differing neighbors, this greater spatial specificity allows the cell to build a much more varied and dynamic topology for differential distributions of macroscopic biological structures.

Several specific mechanisms can be envisioned for these quasi-linear domains, which remarkably are distributed near the radial paths of microtubules. Is there a linear path cut through the actin-bound membrane fences (Figure 1A)? If so, the confinement width should broaden when the cortical actin meshwork is disrupted. Do microtubules peel the cortical actin away from the bilayer and thus create a "tent" of actin-free membrane (Figure 1B), or do they preferentially localize to the well-known folds of macrophages? This should be discernable in electron tomography. Is actin-binding transmembrane protein (ABTP) density spatially dependent on both actin and tubulin (i.e., a scaffolded picket fence; Figure 1C)? In this scaffolded picket fence model, microtubules just below the membrane could break the connections between cortical actin and the ABTP "pickets" in the membrane, clearing a path for diffusion of membrane components along a channel but leaving the cortical actin itself intact and still in reasonable proximity to the membrane for rapid reversal of tubulin-dependent effects. Is the confinement zone itself moving within the membrane, either by diffusion or by attachment to one or more molecular motors (Figure 1D)? In this case, the diffusion would be microscopically isotropic with confinement to 190 nm, but a nanoscale drift in one direction would be superimposed, as, for example, in the Smoluchowski equation (Berezhkovskii et al., 1989). There is precedence for the model of cytoskeletal movement, such as in the radial actin motoring in the immune synapse (Yu et al., 2010). Further experiments will be necessary to fully elucidate the mechanism behind these domains.

The capabilities of superresolution microscopy and other single-molecule techniques may be the key to understanding how directed motion (for example via actomyosin and microtubules) is cooperatively coupled to diffusive motion within the bilayer. Simultaneous three-dimensional superresolution live cell imaging of actin, tubulin, and membrane components, for example, could potentially distinguish directly between the models discussed here. The techniques used by Jaqaman et al. to measure directly collision rates and metastable clustering elegantly add the important fourth dimension of protein-protein interaction missing from most membrane domain studies. Future studies using these techniques will be needed to test the hypothesis that the geometry per se of cytoskeletal confinement plays a significant physiological role for cell signaling.

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REFERENCES

Berezhkovskii, A.M., Makhnovskii, Y.A., and Suris, R.A. (1989). Chem. Phys. *137*, 41–49.

Goswami, D., Gowrishankar, K., Bilgrami, S., Ghosh, S., Raghupathy, R., Chadda, R., Vishwakarma, R., Rao, M., and Mayor, S. (2008). Cell *135*, 1085–1097.

Hess, S.T., Gould, T.J., Gudheti, M.V., Maas, S.A., Mills, K.D., and Zimmerberg, J. (2007). Proc. Natl. Acad. Sci. USA *104*, 17370–17375.

Jaqaman, K., Kuwata, H., Touret, N., Collins, R., Trimble, W.S., Danuser, G., and Grinstein, S. (2011). Cell *146*, this issue, 593–606.

Morone, N., Fujiwara, T., Murase, K., Kasai, R.S., Ike, H., Yuasa, S., Usukura, J., and Kusumi, A. (2006). J. Cell Biol. *174*, 851–862.

Lingwood, D., and Simons, K. (2010). Science *327*, 46–50.

Semrau, S., and Schmidt, T. (2007). Biophys. J. *92*, 613–621.

Yu, C.H., Wu, H.J., Kaizuka, Y., Vale, R.D., and Groves, J.T. (2010). PLoS ONE *5*, e11878.

Meeting the (N-Terminal) End with Acetylation

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Cell-fate decisions are tightly linked to cellular energy status. In this issue, Yi et al. (2011) introduce a mechanism by which Bcl-xL lowers the threshold for apoptosis by suppressing acetyl-CoA production, which, in turn, suppresses the N-alpha-acetylation important for activation of the proapoptotic protease caspase-2.

A cell's decision to die by apoptosis, become quiescent, or proliferate is influenced by the metabolic conditions of the cell and its surrounding tissue. Over the past decade, multiple studies have established direct links between these critical cellular pathways. For example, when glucose levels fluctuate, glucose-sensing pathways transduce signals through the