BioEssays

WILEY-VCH

BioEssays

REVIEW ESSAY OPEN ACCESS

Dynamic Plasma Membrane Topography Linked With Arp2/3 Actin Network Induction During Cell Shape Change

Tony J. C. Harris

Department of Cell & Systems Biology, University of Toronto, Toronto, Canada

Correspondence: Tony J. C. Harris (tony.harris@utoronto.ca)

Received: 20 December 2024 | **Revised:** 13 March 2025 | **Accepted:** 17 March 2025

Funding: This work was funded by the Natural Sciences and Engineering Research Council of Canada RGPIN-2023-04378.

Keywords: Arp2/3 | cell cortex remodeling | cytoskeleton | mechanotransduction | membrane curvature | microenvironment | nucleation promoting factors

ABSTRACT

Recent studies show the importance of mesoscale changes to plasma membrane (PM) topography during cell shape change. Local folding and flattening of the cell surface is mechanosensitive, changing in response to both microenvironment structural elements and intracellular cytoskeletal activities. These topography changes elicit local mechanical signaling events that act in conjunction with molecular signal transduction pathways to remodel the cell cortex. Experimental manipulations of local PM curvature show its sufficiency for recruiting Arp2/3 actin network induction pathways. Additionally, studies of diverse cell shape changes—ranging from neutrophil migration to early Drosophila embryo cleavage to neural stem cell asymmetric division—show that local generation of PM folding is linked with local Arp2/3 actin network induction, which then remodels the PM topography during dynamic control of cell structure. These examples are reviewed in detail, together with known and potential causes of PM topography changes, downstream effects, and higher-order feedback.

1 | Introduction

Since the origin of life, lipid bilayers have functioned reciprocally with genetic instructions, gene products and metabolites. Although cell membranes rely on lipid-synthesizing enzymes encoded by genes, they assemble from pre-existing membrane templates. Membranes also organize gene products by compartmentalizing the cell and by integrating spatial scales. The plasma membrane (PM) has a surface area much larger than any individual protein, and molecularly distinct PM domains act in concert to govern overall cell structure and function [1]. At scales of tissues and organs, PMs connect via cell–cell adhesion complexes [2, 3], and interact with extracellular matrices [4]. A longstanding question is how intracellular and extracellular information intergates at the PM to guide cell shape changes during animal development, physiology and disease states.

The receipt and transduction of signals are central to dynamic PM changes that underlie cell shape change. PM signaling often involves transmembrane receptors that detect extracellular ligands, or forces, and transduce this information to intracellular signaling pathways. This signaling has various effects on the cell, including the generation of filamentous actin (F-actin) cytoskeletal networks that change cell shape through PM associations [5–8]. For example, binding of an extracellular chemoattractant to its receptor can elicit the growth of an Arp2/3-based actin network which applies actin polymerization forces against a broad PM domain to extend a lamellipodial cell protrusion. Signaling from the receptor to the Arp2/3 complex is mediated by small G protein activation which activates nucleation-promoting factors, WASP, or the WAVE regulatory complex (WRC), which in turn bind and activate Arp2/3 complexes. In its active conformation, an Arp2/3 complex binds a pre-existing actin filament and presents a template for new filament polymerization at a 70° angle, resulting

in the growth of a dendritic actin network against the PM [5–8]. Although much has been learned about these signaling pathways and cytoskeletal effects, how they function in cell shape change is still a major topic of investigation.

In addition to molecular changes on either side of the PM, cells also sense and respond to mesoscale deformations of the PM. Indeed, most animal cells display PM folds, protrusions, and invaginations with both inward and outward curvatures [9]. The prevalence of such PM topographies is often underappreciated due to insufficient microscopy resolution, and to oversimplified textbook diagrams showing the PM as flat. A commonly recognized role of PM folding is the maximization of cell surface area for absorptive activity in the gut [10]. More generally, PM folding protects cells from rupture [11], and provides membrane reservoirs that extend quickly as cells change shape [12, 13]. Here, I review the interplay between PM topography and Arp2/3 actin networks contributing to cell shape change.

2 | Determinants of PM Topography

At a basic level, PM topography is influenced by the properties of lipid bilayers. Due to energetically unfavorable interactions between water molecules and lipid hydrocarbon chains, pure lipid bilayers tend to form vesicles, and such vesicles are typically large and smooth relative to the thickness of the bilayer. Close packing of hydrocarbon chains limits deformations in the plane of the bilayer. With lateral compressive stress, membrane area change is minimal, and instead, the membrane bends out-of-plane. Combining this bending with restoring forces results in membrane undulations, which can be flattened by lateral tensile stress [14–16]. Thus, the topography of a membrane depends on the forces applied to it, on its out-of-plane deformability and on its large-scale geometry. The PM can curve inward or outward, and undulating membranes display opposite curvatures at the tops and bottoms of repeated folds (Figure 1A). Opposite curvatures can also co-exist at the same point as saddle-like shapes where surrounding PM connects with a local membrane invagination (e.g., a caveolae or clathrin coated pit) or evagination (e.g., a filopodia or microvilli) (Figure 1A).

Local accumulations of integral and peripheral PM components additionally affect PM topography. The presence of raft-like lipid domains can specify where PM bending occurs due to the distinct deformability of neighboring domains, and to line tension along domain–domain boundaries [17]. PM bending can also occur from an asymmetry of the bilayer from one side to the other due to local clustering of conical or wedge-shaped lipids or integral proteins [18–20]. Moreover, local assemblies of peripheral cytoplasmic proteins generate a variety of PM topographies linked to specific functions [18–21]. For example, in the formation of endocytic pits and actin-based protrusions, the curved structures of BAR domains allow various peripheral membrane proteins to recognize and generate PM curvature [22] (Figure 1B). Local growth of F-actin arrays against the PM generates a variety of cell protrusions, including microvilli, filopodia, lamellipodia, and podosomes [23]. Additionally, interactions of phase-separated molecular condensates with the PM can result in local membrane curvature [20, 24, 25] (Figure 1B). In contrast, increased tension in the plane of the PM flattens PM topographies, as exemplified by the flattening of caveolae for membrane tension buffering [26].

PM topography is also affected by cytoskeletal activities within the cell and microenvironments surrounding the cell. For example, contraction of a cortical actomyosin network can compress its associated PM domain which becomes folded in response (Figure 1C), as observed during cytokinesis of cultured mammalian cells [27] and during polarization of Drosophila neuroblasts [28]. At a distance from such contractile domains, the PM can gain tensile stress and flatten [29] (Figure 1D). As evident during cellularization of the Drosophila embryo, targeted exocytosis can promote domains of PM folding that involve structural support from local actin networks but that might also be promoted by lateral compressive stress of excess membrane being added to a domain of limited size [30]. In addition to actin networks, microtubules emanate to the PM, and microtubule motors can pull the PM inward and generate PM infoldings (Figure 1C), as observed in the *Caenorhabditis elegans* embryo [31–33], the ascidian embryo [34], the immune synapse [35] and the Drosophila embryo [36]. In vivo, cells physically engage various extracellular matrix topographies that can push the PM inward and generate PM folds [37, 38] (Figure 1B). Distinctive PM topographies also arise from cell–cell interactions (Figure 1C). Finger-like actin- or microtubule-based protrusions of one cell can push into another cell, generating curved, double PM configurations for cell–cell adhesion [39] or cell–cell signaling [40]. Moreover, asymmetric cell–cell adhesion forces pull double membranes into one cell during endothelial cell collective migration [41], and epithelial cell division [42]. In contrast, increased hydrostatic pressure within the cell promotes flattening of local PM topography [18, 29] (Figure 1D).

These examples highlight many ways PM topography can change, involving forces in the plane of the membrane or perpendicular to it. Next, I review experiments showing that curved PM topography can induce local assembly of Arp2/3 actin networks.

3 | Effects of PM Topography on Actin Network Induction

Effects of PM topography are clearest in experiments that directly manipulate local PM shape. Specifically, the deposition of various cell types on substrates fabricated with nanoscale surface topographies has shown that PM topography follows substrate topography and that F-actin accumulates at sites of induced PM bending [43]. Actin network associations with curved membranes are also evident from phagocytosis of particles with engineered curvatures [44] and by reconstitution of F-actin polymerization with curved liposomes [45]. Moreover, light-responsive substrates now allow temporal control of local PM topography to test response dynamics [46].

Determinants of F-actin recruitment to PM curvature have been characterized systematically in U2OS cells plated on fabricated substrates [47]. Rod-shaped nanopillars become fully enwrapped by the PM, but F-actin accumulates preferentially at each curved end of the rod. The influence of PM curvature is further evident from greater F-actin recruitment to round nanopillars with

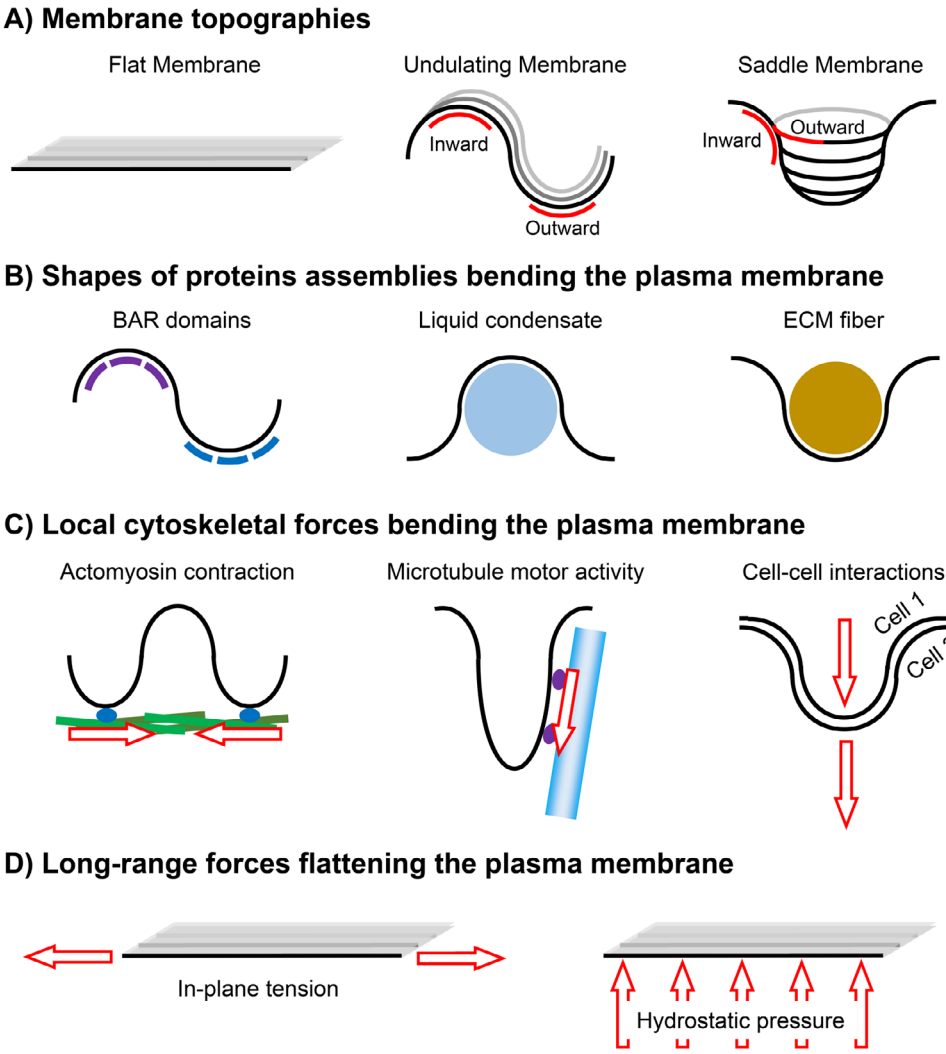

FIGURE 1 | Determinants of PM topography. In each diagram, the PM is shown as black or gray lines, with the cytoplasm below, and the extracellular space above. In the cell–cell interaction diagram, (C), the two cells are labeled. (A) Membrane regions can be flat or curved. Middle, an undulating membrane has folds with inward curvature next to folds with outward curvature (red lines). Right, a local membrane invagination has a saddle-like configuration with both inward bending and outward bending at the same site (red lines). (B) Shapes of protein assemblies can bend associated PM. Left, intracellular assemblies of BAR domain-containing proteins associate with inward and outward bends. Middle, a cytoplasmic condensate linked to inward PM bending. Right, an extracellular matrix (ECM) fiber is associated with outward PM bending. (C) Physical forces (red arrows) generated by local cytoskeletal activities can bend associated PM. Left, contraction of a cortical actomyosin network (green lines) bends PM between attachment sites (blue ovals). Middle, motor movement along a microtubule (blue) bends PM inward via attachment sites (purple ovals). Right, asymmetry of outward pushing forces, or inward pulling forces, across a cell-cell contact bends associated PMs. (D) Flattening of a PM region by in-plane tension from distant cytoskeletal activities (left), and by hydrostatic pressure from the cytosol (right).

smaller diameters, and thus greater curvatures. From diameters of 400 to 100 nm, local F-actin recruitment increases progressively relative to the amount of PM at the pillar. Strikingly, actin networks display cycles of assembly and disassembly at the sites. F-actin accumulation coincides with that of Arp2/3 complexes and depends on Arp2/3 activity, whereas formin activities seem irrelevant. BAR domain proteins of the Toca family (FBP17, Toca1, and Cip4) with known links to Arp2/3 activation, all accumulate at the sites as well, and over-expression of a dominant negative FBP17 construct disrupts the Arp2/3 and F-actin accumulations. In this context, the accumulations appear to be independent of endocytosis or focal adhesion assembly [47]. The central role of BAR domain proteins in the response to nanopillar-induced PM topography [47] is consistent with the results of actin polymerization assays conducted with deformable liposomes to assess the effects of membrane topography [45]. Remarkably, Arp2/3 actin networks also assemble where the PM of Dictyostelium cells enters holes cut out of their substrate [48]. Thus, Arp2/3 actin networks can be locally induced by both the inward bending of PM over substrate pillars and the outward bending of the PM into substrate holes.

These elegant studies established that PM curvatures can locally induce actin networks. I now turn to relationships between PM topographies and actin network inductions during whole-cell shape changes. The focus is on PM deformations that are relatively small and transient. Recent reviews cover the effects of membrane curvature on organizing endocytosis and

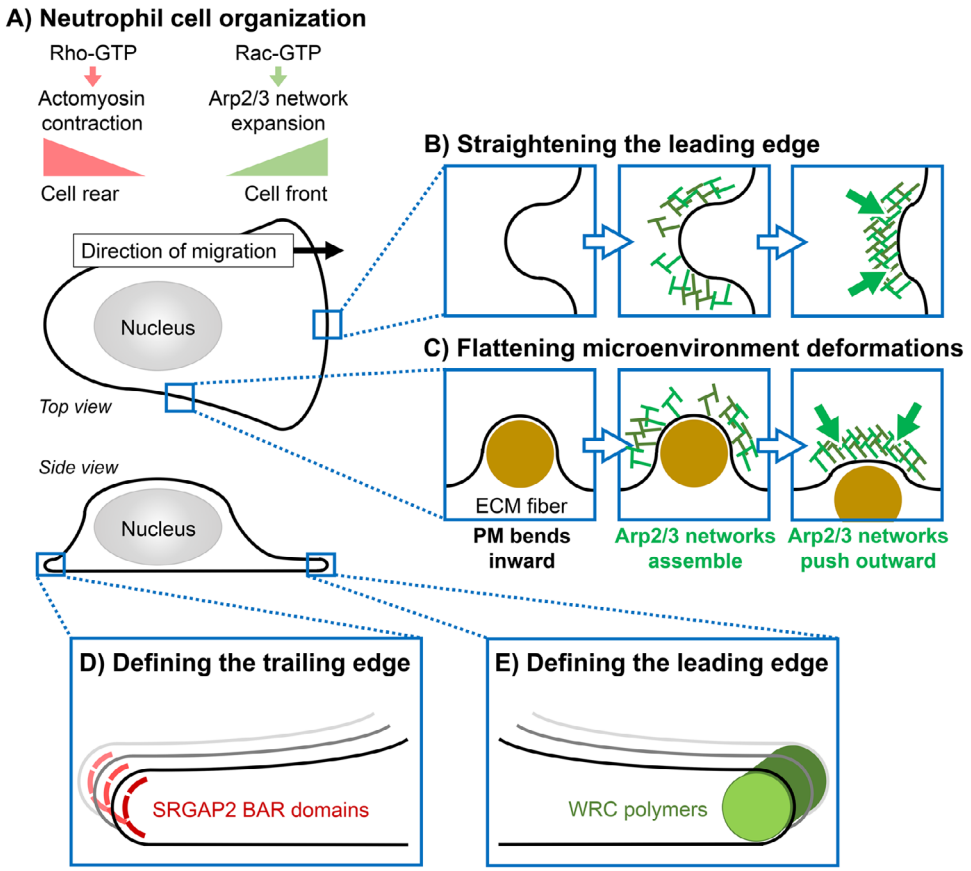

FIGURE 2 | Links between PM topography and Arp2/3 network induction during neutrophil cell migration. In each diagram, the PM is shown as black or gray lines. (A) The overall shape of a migrating neutrophil is shown in the top and side views. A pathway linking Rho-GTP to actomyosin contraction is concentrated at the cell rear. A pathway linking Rac-GTP to Arp2/3 network expansion is concentrated at the cell front, in the direction of cell migration. (B) Local deformation of the leading edge results in curved PM. Arp2/3 networks (two shades of green) assemble at the local PM curvature, polymerize against it, and help straighten the leading edge across the cell front. (C) Cells can be locally deformed by crawling through extracellular matrix (ECM) fibers. Arp2/3 networks assemble at the resulting PM curvature, polymerize against it, and push the ECM fiber away. (D) Where the PM folds back on itself at the trailing edge, the BAR domain of SRGAP2 associates with the curved membrane and helps define the trailing edge. (E) Where the PM folds back on itself at the leading edge, bundled polymers of the WAVE regulatory complex (WRC) associate with the curved membrane and help define the leading edge.

intracellular membranes [20, 49–51], cellular responses to long-range curvatures [52, 53], and F-actin assembly into filopodia and microvilli, finger-like PM extensions with high curvature [10, 54].

4 | Links Between PM Topography and Actin Network Induction as Cells Interact With Their Surroundings

Immune cell migration throughout the body is essential for finding and eliminating pathogens. Decades of study have shown how biochemical signaling pathways convert extracellular chemoattractant cues into an intracellular polarity that deploys force-generating cytoskeletal networks to the cell front and rear. Rac small G protein activity at the front promotes forward growth of an Arp2/3-based lamellipodium, and Rho small G protein signaling at the rear elicits actomyosin-based cortical contraction [55, 56] (Figure 2A). The overall organization of the migratory cell is also affected by physical coordination between these cytoskeleton activities [57]. For example, as Arp2/3 network polymerization pushes the cell front forward, membrane tension elevates along the sides of the cell and hinders the formation of secondary fronts. Actomyosin contraction at the rear also generates cytosolic pressure through the cell, and the balance between rear contraction and front Arp2/3 activity dictates whether migration is driven by the extension of a lamellipodium or a bleb-based protrusion. In coordination with these integrated biochemical and biophysical effects, PM topography contributes to the deployment of cytoskeletal networks to the front, rear, and sides of migrating immune cells. It seems that this combinatorial control enables the cell to navigate its local, physical surroundings while pursuing long-range targets.

How numerous inductions of Arp2/3-based actin networks across the cell front produce a broad lamellipodia with a unified leading edge has been a longstanding question. Patchiness of local network inductions correlate with undulations of the leading edge [58]. Broadening of Arp2/3 network polymerization angles in response to load provides one adaptive mechanism [58, 59], but simulation studies also implicate interplay between sensors of PM curvature and inducers of actin networks in detecting and eliminating local PM undulations [60]. In addition to curvature

sensing BAR domain proteins, the WRC, which mediates Rac small G protein signaling to activate the Arp2/3 complex [5], has also been implicated. A link between the WRC and PM curvature was revealed when neutrophils were depleted of F-actin, a context in which the WRC localized to 230-nm-wide ring-like structures at the necks of membrane invaginations [61]. Using patterned substrates to mimic these invaginations, as well as compression to flatten them, the PM infoldings were shown to be key for WRC recruitment [62]. Notably, the sites have a saddle-like geometry in which local membrane curvature is inward in one orientation and outward in the perpendicular orientation (Figure 1A). This configuration arises where a subregion of the leading edge falls behind surrounding regions, and it has been proposed that WRC recruitment to such sites induces local Arp2/3 networks, which in turn push lagging regions ahead to unify the cell front [61] (Figure 2B). More recently, polymers of the WRC have been linked to another PM topography of the leading edge [62] (Figure 2E). Along the full leading edge, the PM folds back on itself, similar to the crease of folded paper. WRC polymers accumulate along this strip of curved PM and appear to provide structural support along the full leading edge, in addition to activating Arp2/3. Reciprocally, the folded-back curvature along the leading edge promotes the localization of WRC polymers, as shown with experiments that flattened the curvature. Thus, PM curvatures may contribute to unifying the lamellipodia leading edge through both adaptive regulation and positive feedback reinforcement.

Inversely, changes to leading-edge PM topography have been implicated in obstacle avoidance. Wu et al. proposed that collision with an immobile extracellular object would reduce folded-back membrane curvature along the leading edge, as well as WRC localization and Arp2/3-based actin polymerization, thereby stopping lamellipodium induction in response to stiff obstacles [62]. Recruitment of the BAR domain protein Snx33 to indentations of the neutrophil leading edge has also been linked to inhibition of WRC-induced actin polymerization during obstacle avoidance [63].

It is important to recognize that PM topography is not the only determinant of WRC localization to the leading edge. WRC localization to curved membranes is restricted to the cell front by Rac small G protein activity. Within the cell front, Rac small G protein activity has a broader distribution than the WRC, indicating that WRC localization is controlled by a combination of Rac signaling and PM curvature [61, 62]. IRSp53, a BAR domain-containing scaffold protein that couples membrane curvature and actin polymerization in other contexts [64], also functions in linking Rac signaling to the WRC in lamellipodia [65–67], but WRC recruitment to curved membranes can occur independently of IRSp53 [61].

At the cell rear, PM curvature also occurs where the PM bends over on itself to form the trailing edge. This curvature is coupled to the recruitment of the signaling molecule SRGAP2 during neutrophil migration [68] (Figure 2D). A BAR domain within SRGAP2 is key to its localization. With independence from either chemotactic signaling or integrin-based adhesion, the BAR domain localizes to PM curvature generated along the cell rear, or by pulling the PM into a pipette. SRGAP2 functions in recruiting contractile myosin networks to the trailing edge via lipid signaling [68]. It remains to be determined how SRGAP2 localization to curved membranes is restricted to the cell rear. This restriction could involve a co-requirement of Rho signaling at the rear or an inhibition of SRGAP2 localization to the cell front. Intriguingly, the GTPase activating protein (GAP) activity of SRGAP2 specifically inhibits Rac signaling [69], suggesting it might also influence signaling cross-talk between the cell front and rear.

In addition to the cell front and rear, PM topography affects the central cell body. As neutrophils migrate through rough surroundings, microenvironment topography generates PM topography which in turn recruits WASP, another activator of the Arp2/3 complex [5]. Specifically, neutrophil migration over inert beads causes rapid, local PM indentations and WASP accumulations, as does migration over collagen fibers [70]. Arp2/3 and F-actin also accumulate at these sites with dependence on WASP. These topography-induced accumulations seem functionally relevant since the loss of WASP affects migration on nanoridges more than on flat substrates [70]. Dendritic cells display similar behaviors [71]. Whether plated on ridges or poked with a blunted microneedle, WASP accumulates at PM indentations. Further experiments implicated topography-induced Arp2/3 network induction in counteracting compressions from the microenvironment and making room for cell migration [71]. In various non-immune cell types, specialized integrin complexes have been detected at PM indentations generated by patterned substrates, and similar complexes accumulated on ECM fibers in 3D cultures, where they appear to facilitate migration through these complex microenvironments [72]. In addition to locally displacing the topography of microenvironments (Figure 1C), cells are also stretched and compressed as they navigate them, leading to changes in PM topography and adaptive actin network inductions [73–76]. Such dynamic PM topography along the cell body might also alter long-range PM tension that couples cytoskeletal activities at the cell front and rear to coordinate overall neutrophil polarity [77]. As recently reviewed elsewhere, long-range transmission of PM tension is highly context-dependent [57, 78, 79]. Whether it is reversibly dampened by microenvironment-induced PM curvatures, and the adaptive assembly and disassembly of local Arp2/3 networks, is an intriguing question for future studies.

Similar to the WRC, WASP recruitment to curved membranes involves additional input from biochemical signaling. Specifically, WASP accumulations at curved membranes along the cell body are also dependent on Cdc42 small G protein activity biased to the cell front [70]. As cells migrate over populations of beads, WASP is recruited quickly to beads near the cell front but is then lost as the beads become associated with the cell rear. Thus, a combination of membrane infolding and Cdc42 activity seems needed for inducing the WASP-dependent actin networks as the cell body engages its microenvironment. How these PM indentations become populated with Cdc42-dependent WASP rather than Rac-dependent WRC is not fully understood, but it has been proposed that the circular structures of WASP condensates and linear structures of bundled WRC polymers are additional determinants of their distinct localizations [62, 70].

PM topography also has many effects on cell–cell interactions. At immune synapses, T cells generate complex cell–cell interface topographies that are WASP- and Arp2/3-based and enhance cell–cell communication [80, 81]. Moreover, T-cell cytoskeletal

networks respond to topographies of fabricated substrates [82]. Complex PM topographies linked to local Arp2/3 networks also allow phagocytes to internalize large particles through the coordinated actions of multiple interaction sites [83]. During endothelial cell collective migration, asymmetric cytoskeletal forces across cell–cell junctions pull the junctions into one cell and away from the other, resulting in serrated contacts between leader and follower cells [41]. At these contacts, both PMs, linked by cadherin-catenin complexes, are drawn into the follower cell as "cadherin fingers" with high local membrane curvature [84]. BAR domain-containing proteins are recruited to these membranes and regulate junctional endocytosis at the sites [41, 85]. The follower cell PM domain containing the cadherin fingers helps direct follower cell migration, which involves the induction of cryptic lamellipodia from the same PM domain where the cadherin fingers form [84]. Interestingly, the relationship between membrane curvature and Arp2/3 networks seems to be reversed at muscle attachment sites in Drosophila, where Arp2/3-dependent actin polymerization generates a serrated cell–cell contact which confines integrin complexes and promotes heterotypic adhesion [86]. Arp2/3 activity is also required for mammalian podocytes to form arborized cell protrusions that mediate integrin-basement membrane adhesion of the kidney filtration barrier [87]. Overall, the coupling of PM topography changes with actin network inductions seems widespread as cells interact with their surroundings.

5 | Links Between PM Topography and Actin Network Induction as Cells Change Shape From Within

Cells also change shape in response to internal cues, as exemplified by components of the mitotic apparatus providing positional information for shape change during cell division [88]. This coordination also involves PM topography changes, both in a multinucleated (syncytial) system and during the division of mononucleated cells.

The early Drosophila embryo develops as a syncytium, in which synchronously dividing nuclei individually induce reshaping of the cell surface to form dome-like compartments that house individual mitotic apparatuses [89] (Figure 3A). Their individual formation is structurally analogous to cell budding that initiates polar body extrusion from the mouse oocyte [90], but many small compartments form over the one-cell Drosophila embryo surface, and they recede and reform during each mitotic cycle rather than progressing to full cell division. The centrosome provides the spatial cue for inducing growth of the dome-like compartment, which occurs through Arp2/3-based actin polymerization and membrane exocytosis. Induction of the actin networks begins over each centrosome at anaphase, and by interphase of the next cycle, two dome-like compartments each house a daughter nucleus of the preceding mitosis [89]. PM staining of fixed embryos showed that the actin network induction is accompanied by unique PM organization above each centrosome at anaphase [91]. More recent live imaging revealed that each centrosome is associated with a folded PM domain from which PM tubules extend inward toward the centrosome. The focusing of this PM topography above the centrosome coincides with greater numbers of centrosomal MTs at anaphase and telophase, the PM tubules associate closely with centrosomal MTs, and the PM tubules require both centrosome integrity and the centrosome-directed MT motor dynein. Thus, at the onset of compartment growth, the centrosome alters local PM topography from within the cell [36] (Figure 3A).

The local, centrosome-generated PM topography of the one-cell Drosophila embryo is linked with both Arp2/3 network induction and exocytic factors required for growth of the dome-like compartment [36, 89]. A Doc-family Rac-GEF (Sponge), Rac-GTP, WRC, Arp2/3, and F-actin are all enriched at the PM folds and tubules relative to surrounding PM, and Rab8 exocytic vesicles co-accumulate with PM tubules in proximity to the centrosome. Recruitment of the Arp2/3 actin network induction pathway requires centrosome integrity and dynein activity, but more widespread PM folding at other cell cycle stages, or with experimentally reduced PM tension, is insufficient for recruiting the pathway to ectopic sites, suggesting that normal Arp2/3 recruitment occurs through a combination of centrosome-emitted inductive signals and centrosome-organized PM topography [36]. Arp2/3 network growth is required for the PM domain to unfold and expand laterally into an actin cap [36], and for subsequent formation of the dome-like compartment [92] (Figure 3A), which involves both bending and cytoplasmic swelling of the compartment [93]. Loss of Arp2/3 activity results in abnormally persistent associations of PM infoldings with the centrosome, indicating a force balance between centrosome-directed pulling activity and outwardly-directed pushing activity, a balance that normally tips in favor of Arp2/3-based expansion of the cortical domain [36]. As the actin cap grows away from the centrosome, it also displays topography changes associated with a composite cytoskeletal network. Bulging subdomains of the cap grow laterally and flatten through Arp2/3 activity while engaging intervening, formin-dependent F-actin bundles that assemble around the bottom edges of the bulges [94]. Overall, the formation of the dome-like compartments is similar to lamellipodia of immune cells in several ways: (i) coupling of PM topography change with Arp2/3 actin network induction, (ii) the combination of PM topography and separate signals for the induction, and (iii) the conversion of local membrane curvatures into a broad, unified structure by Arp2/3 actin network growth. BAR domain-containing proteins are needed for the growth of the dome-like compartments in Drosophila [95–97], but specific involvement in coupling PM topography to Arp2/3 network induction has not been reported.

PM topography changes also contribute to mononucleated cell division. For example, the assembly of the actomyosin-based cytokinetic ring generates the cytokinetic furrow, and inward bending of the furrow can promote actomyosin flow into a thinner, more focused ring [98]. Ring constriction generates intercellular pressure, which can be relieved by outward PM blebbing at the poles of the cell [99]. During asymmetric cell division, the two poles of the cell gain distinct properties and undergo more complex cell shape changes that result in two daughter cells with different sizes [100] (Figure 3B). In Drosophila larval neuroblasts, the flow of an actomyosin network to one pole generates a reservoir of PM folds that contribute to the subsequent enlargement of the daughter cell relative to its sister during cytokinesis [28]. PM folding within this cortical domain is also coupled with Arp2/3 network induction. The WRC enriches at the cortex in

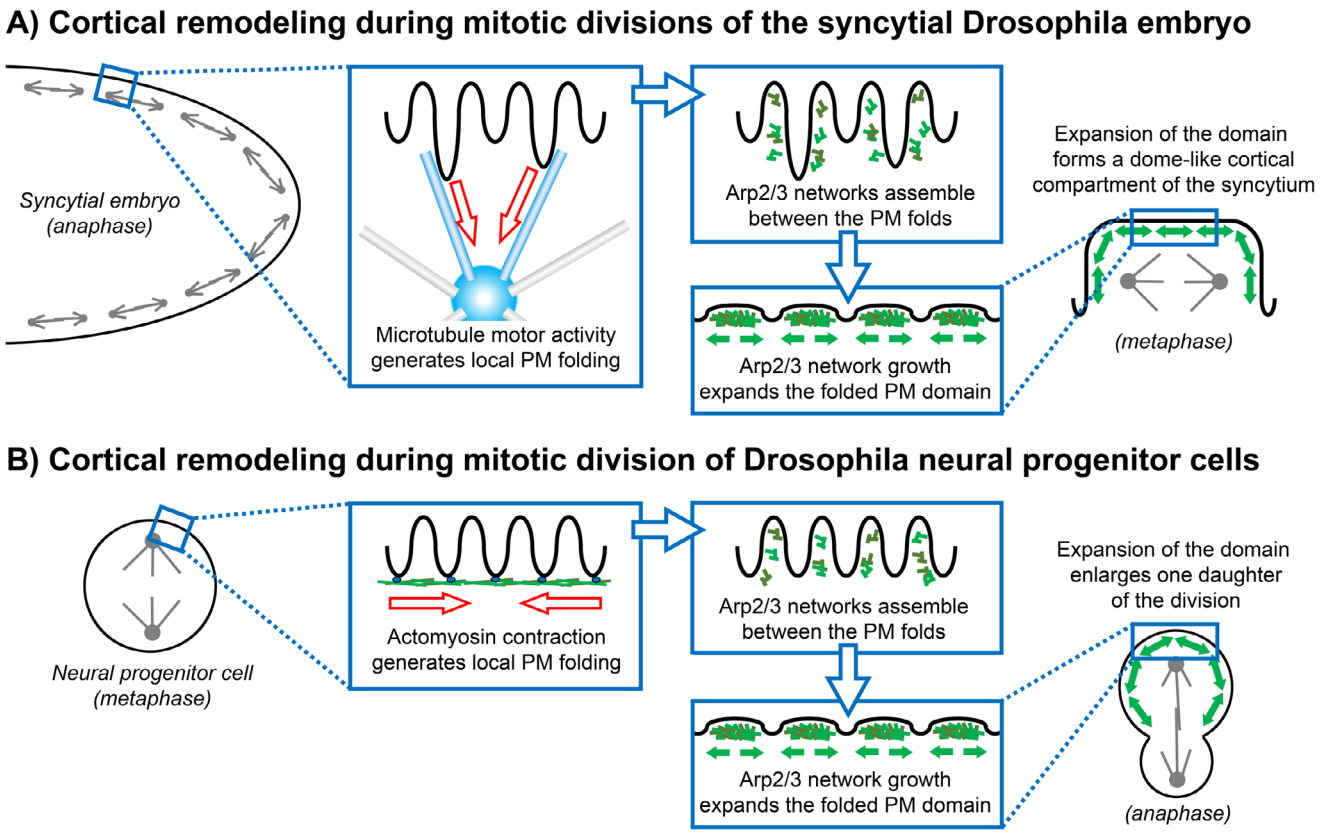

FIGURE 3 | Links between PM topography and Arp2/3 network induction during cell shape changes of the syncytial Drosophila embryo and of Drosophila neural progenitor cells. In each diagram, the PM is shown as black lines. Mitotic spindles are shown in gray within the cells. Explanatory text is within the figure.

proximity to the folds, a localization requiring Pins, a molecular link between the spindle and cortex. Downstream Arp2/3 activity remodels PM fold structure, promotes cortex-centrosome separation, and stabilizes cell shape as asymmetric division occurs [101]. Moreover, actin polymerization accompanies the asymmetric growth of the larger daughter cell cortex during the division of both Drosophila larval neuroblasts and Drosophila sensory organ precursor cells. During asymmetric sensory organ precursor cell division, this cortical actin polymerization is Arp2/3-based and physically supports the asymmetrically enlarged cortex of the one daughter [102]. Taken together, it appears that local actomyosin activity generates a domain of PM folds, which act both as membrane reservoirs and as sites of Arp2/3 network growth for the preferential expansion of one daughter cell cortex during asymmetric cell division (Figure 3B).

Whether PM folding promoted by centrosomal MTs affects cortex growth during mononucleated cell division remains unknown. Intriguingly, oriented cell division in the ascidian embryo epidermis involves a physical linkage between centrosomal MTs and a PM invagination [34], and during asymmetric division of the *C. elegans* one-cell embryo, centrosomal MTs also pull PM tubules inward [31–33]. However, location-dependent interplay between centrosomal and actomyosin effects would likely occur. Local PM folding within an actomyosin domain could conceivably be enhanced by additional inward pulling forces of centrosomal microtubules, but more global generation PM tension by actomyosin activity can hinder the ability of centrosomal microtubules to pull PM tubules inward [31, 36]. For MTs and actomyosin networks to affect PM topography, cytoskeleton-membrane linker proteins, such as NuMA complexes [103] or ERM proteins [104], would also be needed.

6 | Possible Ways PM Topographies Could be Linked to Actin Network Inductions

A common way PM topography is linked to actin network induction is through proteins containing BAR domains [20–22]. Local curvature of the PM can be recognized by the curvature of the BAR domain and connected protein domains can mediate effects on actin networks. This basic adaptor activity of a single multidomain protein is enhanced by protein–protein associations among such proteins, and by promotion of these associations by local membrane curvature. Specifically, membrane topography can promote side-by-side stacking of elongated BAR domain proteins. This effect is related to nematic ordering, during which elements gain alignment due to their elongated structure and confining surroundings [105]. Confinement by membrane topography seems to promote alignment of BAR domain proteins into larger assemblies, and the coordinated curvature of these assemblies can feedback to promote membrane curvature [106–108]. To allow membrane dynamics, such mutual reinforcement must be reversible. One regulatory mechanism can arise from the induction of local actin polymerization forces capable of flattening the initial PM fold. This flattening could terminate

curvature-induced signaling. Alternately, waves of membrane curvature and actin polymerization can travel across the PM through cycles of displaced PM gaining curvature, positive feedback of BAR domains enhancing the new curvature, and subsequent actin network growth displacing the curvature [109]. It is tempting to speculate that in addition to discrete push-off events, such topography-responsive waves could help the body of a migratory cell pass through complex microenvironments. The ability of coupled positive and negative feedback loops to generate dynamic patterns across space and time is well-established [110], and coupling of biochemical feedback loops has also been implicated in actin network organization by membrane topography [111]. During natural cell shape changes, however, it remains unclear how effects of PM topography are modified by positive and negative feedback loops.

Mesoscale coupling of protein assemblies with curved membranes can also involve proteins that lack BAR domains. Liquid-like molecular condensates can gain curved surfaces and display dynamic interactions with membranes [20, 24]. The curved surface of a phase-separated liquid arises from the surface tension of minimizing surface exposure to surrounding matter [112]. More conformations are possible when components of a liquid condensate also have an affinity for a lipid bilayer, ranging from membrane-associated films to membrane-associated spheres, and condensates have been observed to first "wet" the PM by forming a thin film, and subsequently round up in association with the membrane, resulting in membrane bending [20, 24]. General rules governing relationships between liquid condensates and membranes remain unclear, but concepts from studies of BAR domain proteins may be relevant. For example, positive feedback between a condensate and membrane domain could generate curvature of both. At the other extreme, a condensate with relatively stable curvature may simply recognize pre-existing sites of PM curvature. How the association of a molecular condensate with a curved membrane could be coupled with actin network induction remains unclear. Intriguingly, Arp2/3 actin networks associate preferentially with curved membranes in assays with no other components suggesting they have curved structural features [113], and as discussed, spherical WASP condensates and bundled WRC polymers have curvatures with the potential to associate with specific PM topographies [62, 70].

Another way membrane folding could enhance actin network induction is by increasing the number of membrane-associated effectors near a separate signaling molecule source, such as the centrosome. Compared with three-dimensional space, the restriction of signaling molecules to the two-dimensional plane of a membrane can enhance their associations by reducing their degrees of freedom [114, 115]. However, the effects of upstream signaling molecules originating from a site away from the PM would be limited by the amount of PM in proximity to the signaling site. This limitation could be reduced by PM folding. Similar to how microvilli can increase the amount of PM available for absorptive activity in a PM domain, PM folding could enhance the amount of membrane-associated effectors near the signaling source. The core concept of fractal geometry is relevant [116]. A two-dimensional membrane can gain some three-dimensionality by folding. Indeed, single-molecule imaging has shown that PM proteins reside longer in a subdomain of the cell surface when the PM is highly folded [117, 118]. Thus, folded PM topography has the potential to increase the number of effectors near a signaling source, while also promoting membrane-associated interactions of actin network activators for the growth of a new cortical domain.

7 | Conclusions and Outlook

It has long been recognized that lipid membranes are critical for compartmentalizing gene products within the cell. More recent attention has focused on membrane topography. PM folding can provide both membrane reservoirs for rapid cell shape change and signaling platforms for organizing cortical actin domains. PM topography is affected physically by mesoscale changes inside or outside the cell and helps coordinate inductions of actin networks for cell shape change. The interplay of molecular and mechanical biology evident from studies of PM topography also has broader implications. It is becoming clear that cells are packed with membrane systems, cytoskeletal networks, and molecular condensates, all with distinct molecular compositions and material properties [119–122]. Packing of these materials would generate various interfaces among them, and these interfaces might change their topographies in distinctive ways as cells change shape. An intriguing possibility is that molecular signaling pathways coordinate with a broad variety of mesoscale topography changes during cell and tissue morphogenesis.

Author Contributions

The author was the only contributor to the writing of the essay.

Acknowledgments

I thank Rudi Winklbauer and Rodrigo Fernandez-Gonzalez for their valuable comments on the manuscript, and the reviewers for their thoughtful suggestions. Research in my lab on the topic is funded by a Natural Sciences and Engineering Research Council of Canada Discovery Grant (RGPIN-2023-04378).

Conflicts of Interest

The author declares no conflicts of interest.

Data Availability Statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study

References

1. W. J. Nelson, "Adaptation of Core Mechanisms to Generate Cell Polarity," *Nature* 422 (2003): 766–76774.

2. T. J. Harris and U. Tepass, "Adherens Junctions: From Molecules to Morphogenesis," *Nature Reviews Molecular Cell Biology* 11 (2010): 502–514.

3. C. Zihni, C. Mills, K. Matter, and M. S. Balda, "Tight Junctions: From Simple Barriers to Multifunctional Molecular Gates," *Nature Reviews Molecular Cell Biology* 17 (2016): 564–580.

4. K. M. Yamada and M. Sixt, "Mechanisms of 3D Cell Migration," *Nature Reviews Molecular Cell Biology* 20 (2019): 738–752.

5. A. M. Gautreau, F. E. Fregoso, G. Simanov, and R. Dominguez, "Nucleation, Stabilization, and Disassembly of Branched Actin Networks," *Trends in Cell Biology* 32 (2022): 421–432.

6. V. Papalazarou and L. M. Machesky, "The Cell Pushes Back: The Arp2/3 Complex Is a Key Orchestrator of Cellular Responses to Environmental Forces," *Current Opinion in Cell Biology* 68 (2021): 37–44.

7. J. D. Rotty, C. Wu, and J. E. Bear, "New Insights Into the Regulation and Cellular Functions of the ARP2/3 Complex," *Nature Reviews Molecular Cell Biology* 14 (2013): 7–12.

8. S. Buracco, S. Claydon, and R. Insall, "Control of Actin Dynamics During Cell Motility," *F1000Research* 8 (2019): F1000 Faculty Rev–1977.

9. I. Parmryd and B. Onfelt, "Consequences of Membrane Topography," *The FEBS Journal* 280 (2013): 2775–2784.

10. C. Sauvanet, J. Wayt, T. Pelaseyed, and A. Bretscher, "Structure, Regulation, and Functional Diversity of Microvilli on the Apical Domain of Epithelial Cells," *Annual Review of Cell and Developmental Biology* 31 (2015): 593–621.

11. A. L. Le Roux, X. Quiroga, N. Walani, M. Arroyo, et al., "The Plasma Membrane as a Mechanochemical Transducer," *Philosophical Transactions of the Royal Society of London Series B: Biological Sciences* 374 (2019): 20180221.

12. L. Figard and A. M. Sokac, "A Membrane Reservoir at the Cell Surface," *Bioarchitecture* 4 (2014): 39–46.

13. M. Goudarzi, K. Tarbashevich, K. Mildner, et al., "Bleb Expansion in Migrating Cells Depends on Supply of Membrane from Cell Surface Invaginations," *Developmental Cell* 43 (2017): 577–587.e5.

14. W. Helfrich, "Elastic Properties of Lipid Bilayers: Theory and Possible Experiments," *Zeitschrift fur Naturforschung. Teil C: Biochemie, Biophysik, Biologie, Virologie* 28 (1973): 693–703.

15. R. Lipowsky, "The Conformation of Membranes," *Nature* 349 (1991): 475–481.

16. Z. Shi and T. Baumgart, "Dynamics and Instabilities of Lipid Bilayer Membrane Shapes," *Advances in Colloid and Interface Science* 208 (2014): 76–88.

17. S. Komura and D. Andelman, "Physical Aspects of Heterogeneities in Multi-Component Lipid Membranes," *Advances in Colloid and Interface Science* 208 (2014): 34–46.

18. J. C. Stachowiak, F. M. Brodsky, and E. A. Miller, "A Cost–Benefit Analysis of the Physical Mechanisms of Membrane Curvature," *Nature Cell Biology* 15 (2013): 1019–1027.

19. I. K. Jarsch, F. Daste, and J. L. Gallop, "Membrane Curvature in Cell Biology: An Integration of Molecular Mechanisms," *Journal of Cell Biology* 214 (2016): 375–387.

20. D. H. Johnson, O. H. Kou, N. Bouzos, and W. F. Zeno, "Protein–Membrane Interactions: Sensing and Generating Curvature," *Trends in Biochemical Sciences* 49 (2024): 401–416.

21. N. S. Gov, "Guided by Curvature: Shaping Cells by Coupling Curved Membrane Proteins and Cytoskeletal Forces," *Philosophical Transactions of the Royal Society of London Series B: Biological Sciences* 373 (2018): 20170115.

22. M. Simunovic, E. Evergren, A. Callan-Jones, and P. Bassereau, "Curving Cells Inside and Out: Roles of BAR Domain Proteins in Membrane Shaping and Its Cellular Implications," *Annual Review of Cell and Developmental Biology* 35 (2019): 111–129.

23. K. Rottner and M. Schaks, "Assembling Actin Filaments for Protrusion," *Current Opinion in Cell Biology* 56 (2019): 53–63.

24. Y. Wang, S. Li, M. Mokbel, et al., "Biomolecular Condensates Mediate Bending and Scission of Endosome Membranes," *Nature* 634 (2024): 1204–1210.

25. A. Mangiarotti and R. Dimova, "Biomolecular Condensates in Contact with Membranes," *Annual Review of Biophysics* 53 (2024): 319–341.

26. B. Sinha, D. Köster, R. Ruez, et al., "Cells Respond to Mechanical Stress by Rapid Disassembly of Caveolae," *Cell* 144 (2011): 402–413.

27. R. Alonso-Matilla, A. R. Lam, and T. P. Miettinen, "Cell-Intrinsic Mechanical Regulation of Plasma Membrane Accumulation at the Cytokinetic Furrow," *Proceedings of the National Academy of Sciences (PNAS) U S A* 121 (2024): 2320769121.

28. B. LaFoya and K. E. Prehoda, "Consumption of a Polarized Membrane Reservoir Drives Asymmetric Membrane Expansion During the Unequal Divisions of Neural Stem Cells," *Developmental Cell* 58 (2023): 993–1003.e3.

29. N. C. Gauthier, T. A. Masters, and M. P. Sheetz, "Mechanical Feedback Between Membrane Tension and Dynamics," *Trends in Cell Biology* 22 (2012): 527–535.

30. L. Figard, M. Wang, L. Zheng, et al., "Membrane Supply and Demand Regulates F-Actin in a Cell Surface Reservoir," *Developmental Cell* 37 (2016): 267–278.

31. S. Redemann, J. Pecreaux, N. W. Goehring, et al., "Membrane Invaginations Reveal Cortical Sites That Pull on Mitotic Spindles in One-Cell C. elegans Embryos," *PLoS ONE* 5 (2010): 12301.

32. Y. L. B. Chapa, M. Hamanaka, A. Wray, et al., "Polar Relaxation by Dynein-Mediated Removal of Cortical Myosin II," *Journal of Cell Biology* 219 (2020): 201903080.

33. Y. C. Tse, A. Piekny, and M. Glotzer, "Anillin Promotes Astral Microtubule-Directed Cortical Myosin Polarization," *Molecular Biology of the Cell* 22 (2011): 3165–3175.

34. T. Negishi, N. Miyazaki, K. Murata, et al., "Physical Association Between a Novel Plasma-Membrane Structure and Centrosome Orients Cell Division," *Elife* 5 (2016): 16550.

35. J. Yi, X. Wu, A. H. Chung, et al., "Centrosome Repositioning in T Cells Is Biphasic and Driven by Microtubule End-On Capture-Shrinkage," *Journal of Cell Biology* 202 (2013): 779–792.

36. R. Tam and T. J. C. Harris, "Centrosome-Organized Plasma Membrane Infoldings Linked to Growth of a Cortical Actin Domain," *Journal of Cell Biology* 223 (2024): 202403115.

37. G. Ventura and J. Sedzinski, "Emerging Concepts on the Mechanical Interplay Between Migrating Cells and Microenvironment in Vivo," *Frontiers in Cell and Developmental Biology* 10 (2022): 961460.

38. S. Azadi, "The Microenvironment and Cytoskeletal Remodeling in Tumor Cell Invasion," *International Review of Cell and Molecular Biology* 356 (2020): 257–289.

39. V. Vasioukhin, C. Bauer, M. Yin, and E. Fuchs, "Directed Actin Polymerization Is the Driving Force for Epithelial Cell–Cell Adhesion," *Cell* 100 (2000): 209–219.

40. M. Inaba, M. Buszczak, and Y. M. Yamashita, "Nanotubes Mediate Niche–Stem-Cell Signalling in the Drosophila Testis," *Nature* 523 (2015): 329–332.

41. T. S. Malinova and S. Huveneers, "Sensing of Cytoskeletal Forces by Asymmetric Adherens Junctions," *Trends in Cell Biology* 28 (2018): 328–341.

42. S. Herszterg, D. Pinheiro, and Y. Bellaïche, "A Multicellular View of Cytokinesis in Epithelial Tissue," *Trends in Cell Biology* 24 (2014): 285–293.

43. H. Y. Lou, W. Zhao, Y. Zeng, and B. Cui, "The Role of Membrane Curvature in Nanoscale Topography-Induced Intracellular Signaling," *Accounts of Chemical Research* 51 (2018): 1046–1053.

44. M. Clarke, U. Engel, J. Giorgione, et al., "Curvature Recognition and Force Generation in Phagocytosis," *BMC Biology* 8 (2010): 154.

45. K. Takano, K. Toyooka, and S. Suetsugu, "EFC/F-BAR Proteins and the N-WASP–WIP Complex Induce Membrane Curvature-Dependent Actin Polymerization," *EMBO Journal* 27 (2008): 2817–2828.

46. S. De Martino, W. Zhang, L. Klausen, et al., "Dynamic Manipulation of Cell Membrane Curvature by Light-Driven Reshaping of Azopolymer," *Nano Letters* 20 (2020): 577–584.

47. H. Y. Lou, W. Zhao, X. Li, et al., "Membrane Curvature Underlies Actin Reorganization in Response to Nanoscale Surface Topography,"

Proceedings of the National Academy of Sciences of the United States of America 116 (2019): 23143–23151.

48. M. Jasnin, M. Ecke, W. Baumeister, and G. Gerisch, "Actin Organization in Cells Responding to a Perforated Surface, Revealed by Live Imaging and Cryo-Electron Tomography," *Structure (London, England)* 24 (2016): 1031–1043.

49. M. M. Kessels and B. Qualmann, "Interplay Between Membrane Curvature and the Actin Cytoskeleton," *Current Opinion in Cell Biology* 68 (2021): 10–19.

50. M. M. Kozlov and J. W. Taraska, "Generation of Nanoscopic Membrane Curvature for Membrane Trafficking," *Nature Reviews Molecular Cell Biology* 24 (2023): 63–78.

51. R. C. Cail and D. G. Drubin, "Membrane Curvature as a Signal to Ensure Robustness of Diverse Cellular Processes," *Trends in Cell Biology* 33 (2023): 427–441.

52. K. S. Cannon, B. L. Woods, and A. S. Gladfelter, "The Unsolved Problem of How Cells Sense Micron-Scale Curvature," *Trends in Biochemical Sciences* 42 (2017): 961–976.

53. L. Pieuchot, J. Marteau, A. Guignandon, et al., "Curvotaxis Directs Cell Migration Through Cell-Scale Curvature Landscapes," *Nature Communications* 9 (2018): 3995.

54. T. C. A. Blake and J. L. Gallop, "Filopodia in Vitro and in Vivo," *Annual Review of Cell and Developmental Biology* 39 (2023): 307–329.

55. K. F. Swaney, C. H. Huang, and P. N. Devreotes, "Eukaryotic Chemotaxis: A Network of Signaling Pathways Controls Motility, Directional Sensing, and Polarity," *Annual Review of Biophysics* 39 (2010): 265–289.

56. F. Wang, "The Signaling Mechanisms Underlying Cell Polarity and Chemotaxis," *Cold Spring Harbor Perspectives in Biology* 1 (2009): a002980.

57. H. De Belly and O. D. Weiner, "Follow the Flow: Actin and Membrane Act as an Integrated System to Globally Coordinate Cell Shape and Movement," *Current Opinion in Cell Biology* 89 (2024): 102392.

58. R. M. Garner and J. A. Theriot, "Leading Edge Maintenance in Migrating Cells Is an Emergent Property of Branched Actin Network Growth," *Elife* 11 (2022): 74389.

59. J. Mueller, G. Szep, M. Nemethova, et al., "Load Adaptation of Lamellipodial Actin Networks," *Cell* 171 (2017): 188–200.e16.

60. R. K. Sadhu, A. Iglič, and N. S. Gov, "A Minimal Cell Model for Lamellipodia-Based Cellular Dynamics and Migration," *Journal of Cell Science* 136 (2023): jcs260744.

61. A. Pipathsouk, R. M. Brunetti, J. P. Town, et al., "The WAVE Complex Associates With Sites of Saddle Membrane Curvature," *Journal of Cell Biology* 220 (2021): 202003086.

62. M. Wu, P. Marchando, K. Meyer, et al., "The WAVE Complex Forms Linear Arrays at Negative Membrane Curvature to Instruct Lamellipodia Formation," *BioRxiv* (2024).

63. E. Sitarska, S. D. Almeida, M. S. Beckwith, et al., "Sensing Their Plasma Membrane Curvature Allows Migrating Cells to Circumvent Obstacles," *Nature Communications* 14 (2023): 5644.

64. S. Ahmed, W. I. Goh, and W. Bu, "I-BAR Domains, IRSp53 and Filopodium Formation," *Seminars in Cell & Developmental Biology* 21 (2010): 350–356.

65. H. Miki, H. Yamaguchi, S. Suetsugu, and T. Takenawa, "IRSp53 Is an Essential Intermediate Between Rac and WAVE in the Regulation of Membrane Ruffling," *Nature* 408 (2000): 732–735.

66. W. Abou-Kheir, B. Isaac, H. Yamaguchi, and D. Cox, "Membrane Targeting of WAVE2 Is Not Sufficient for WAVE2-Dependent Actin Polymerization: A Role for IRSp53 in Mediating the Interaction Between Rac and WAVE2," *Journal of Cell Science* 121 (2008): 379–390.

67. S. Suetsugu, S. Kurisu, T. Oikawa, et al., "Optimization of WAVE2 Complex-Induced Actin Polymerization by Membrane-Bound IRSp53, PIP(3), and Rac," *Journal of Cell Biology* 173 (2006): 571–585.

68. C. Ren, Q. Yuan, M. Braun, et al., "Leukocyte Cytoskeleton Polarization Is Initiated by Plasma Membrane Curvature From Cell Attachment," *Developmental Cell* 49 (2019): 206–219.e7.

69. B. Lucas and J. Hardin, "Mind the (sr)GAP—Roles of Slit-Robo GAPs in Neurons, Brains and Beyond," *Journal of Cell Science* 130 (2017): 3965–3974.

70. R. M. Brunetti, G. Kockelkoren, P. Raghavan, et al., "WASP Integrates Substrate Topology and Cell Polarity to Guide Neutrophil Migration," *Journal of Cell Biology* 221 (2022): 30.

71. F. Gaertner, P. Reis-Rodrigues, I. de Vries, et al., "WASp Triggers Mechanosensitive Actin Patches to Facilitate Immune Cell Migration in Dense Tissues," *Developmental Cell* 57 (2022): 47–62.e9.

72. W. Zhang, C. H. Lu, M. L. Nakamoto, et al., "Curved Adhesions Mediate Cell Attachment to Soft Matrix Fibres in Three Dimensions," *Nature Cell Biology* 25 (2023): 1453–1464.

73. X. Quiroga, N. Walani, A. Disanza, et al., "A Mechanosensing Mechanism Controls Plasma Membrane Shape Homeostasis At the Nanoscale," *ELife* 12 (2023): 72316.

74. K. Tsujita, T. Takenawa, and T. Itoh, "Feedback Regulation between Plasma Membrane Tension and Membrane-Bending Proteins Organizes Cell Polarity during Leading Edge Formation," *Nature Cell Biology* 17 (2015): 749–758.

75. A. Echarri, D. M. Pavón, S. Sánchez, et al., "An Abl-FBP17 Mechanosensing System Couples Local Plasma Membrane Curvature and Stress Fiber Remodeling During Mechanoadaptation," *Nature Communications* 10 (2019): 5828.

76. M. Kapustina, D. Li, J. Zhu, et al., "Changes in Cell Surface Excess are Coordinated With Protrusion Dynamics During 3D Motility," *Biophysical Journal* 122 (2023): 3656–3677.

77. H. De Belly, S. Yan, H. Borja da Rocha, et al., "Cell Protrusions and Contractions Generate Long-Range Membrane Tension Propagation," *Cell* 186 (2023): 3049–3061.e15.

78. A. Ghisleni and N. C. Gauthier, "Mechanotransduction through Membrane Tension: It's All About Propagation?," *Current Opinion in Cell Biology* 86 (2024): 102294.

79. Q. Yan, C. Gomis Perez, and E. Karatekin, "Cell Membrane Tension Gradients, Membrane Flows, and Cellular Processes," *Physiology (Bethesda, Md.)* 39 (2024): 231–245.

80. M. de Jesus, A. H. Settle, D. Vorselen, T. K. Gaetjens, et al. 2024, "Single-Cell Topographical Profiling of the Immune Synapse Reveals a Biomechanical Signature of Cytotoxicity," *Science Immunology* 9: adj2898.

81. F. Tamzalit, M. S. Wang, W. Jin, et al., "Interfacial Actin Protrusions Mechanically Enhance Killing by Cytotoxic T Cells," *Science Immunology* 4 (2019): aav5445.

82. B. A. Wheatley, I. Rey-Suarez, M. J. Hourwitz, et al., "Nanotopography Modulates Cytoskeletal Organization and Dynamics during T Cell Activation," *Molecular Biology of the Cell* 33 (2022): ar88.

83. D. Vorselen, S. R. Barger, Y. Wang, et al., "Phagocytic 'Teeth' and Myosin-II 'Jaw' Power Target Constriction During Phagocytosis," *Elife* 10 (2021): 68627.

84. A. Hayer, L. Shao, M. Chung, et al., "Engulfed Cadherin Fingers Are Polarized Junctional Structures Between Collectively Migrating Endothelial Cells," *Nature Cell Biology* 18 (2016): 1311–1323.

85. T. S. Malinova, A. Angulo-Urarte, J. Nüchel, et al., "A Junctional PACSIN2/EHD4/MICAL-L1 Complex Coordinates VE-Cadherin Trafficking for Endothelial Migration and Angiogenesis," *Nature Communications* 12 (2021): 2610.

86. T. Chen, C. H. Fernández-Espartero, A. Illand, et al., "Actin-Driven Nanotopography Promotes Stable Integrin Adhesion Formation in Developing Tissue," *Nature Communications* 15 (2024): 8691.

87. C. Schell, B. Sabass, M. Helmstaedter, et al., "ARP3 Controls the Podocyte Architecture at the Kidney Filtration Barrier," *Developmental Cell* 47 (2018): 741–757.e8.

88. G. von Dassow, "Concurrent Cues for Cytokinetic Furrow Induction in Animal Cells," *Trends in Cell Biology* 19 (2009): 165–173.

89. R. Tam and T. J. C. Harris, "Reshaping the Syncytial Drosophila Embryo With Cortical Actin Networks: Four Main Steps of Early Development," *Results and Problems in Cell Differentiation* 71 (2024): 67–90.

90. J. Uraji, K. Scheffler, and M. Schuh, "Functions of Actin in Mouse Oocytes at a Glance," *Journal of Cell Science* 131 (2018): jcs218099.

91. R. M. Warn, R. Magrath, and S. Webb, "Distribution of F-Actin During Cleavage of the Drosophila Syncytial Blastoderm," *Journal of Cell Biology* 98 (1984): 156–162.

92. V. Stevenson, A. Hudson, L. Cooley, and W. E. Theurkauf, "Arp2/3-Dependent Psuedocleavage Furrow Assembly in Syncytial Drosophila Embryos," *Current Biology* 12 (2002): 705–711.

93. Y. Zhang, J. C. Yu, T. Jiang, et al., "Collision of Expanding Actin Caps With Actomyosin Borders for Cortical Bending and Mitotic Rounding in a Syncytium," *Developmental Cell* 45 (2018): 551–564.e4.

94. T. Jiang and T. J. C. Harris, "Par-1 Controls the Composition and Growth of Cortical Actin Caps During Drosophila Embryo Cleavage," *Journal of Cell Biology* 218 (2019): 4195–4214.

95. A. Sherlekar and R. Rikhy, "Syndapin Promotes Pseudocleavage Furrow Formation by Actin Organization in the Syncytial Drosophila Embryo," *Molecular Biology of the Cell* 27 (2016): 2064–2079.

96. A. Sherlekar, G. Mundhe, P. Richa, et al., "F-BAR Domain Protein Syndapin Regulates Actomyosin Dynamics During Apical Cap Remodeling in Syncytial Drosophila Embryos," *Journal of Cell Science* 133 (2020): jcs235846.

97. F. F. Rodrigues, W. Shao, and T. J. Harris, "The Arf GAP Asap Promotes Arf1 Function at the Golgi for Cleavage Furrow Biosynthesis in Drosophila," *Molecular Biology of the Cell* 27 (2016): 3143–3155.

98. J. F. Dorn, L. Zhang, T. T. Phi, et al., "A Theoretical Model of Cytokinesis Implicates Feedback Between Membrane Curvature and Cytoskeletal Organization in Asymmetric Cytokinetic Furrowing," *Molecular Biology of the Cell* 27 (2016): 1286–1299.

99. J. Sedzinski, M. Biro, A. Oswald, et al., "Polar Actomyosin Contractility Destabilizes the Position of the Cytokinetic Furrow," *Nature* 476 (2011): 462–466.

100. E. Gallaud, T. Pham, and C. Cabernard, "Drosophila Melanogaster Neuroblasts: A Model for Asymmetric Stem Cell Divisions," *Results and Problems in Cell Differentiation* 61 (2017): 183–210.

101. G. Cazzagon, C. Roubinet, and B. Baum, "Polarized SCAR and the Arp2/3 Complex Regulate Apical Cortical Remodeling in Asymmetrically Dividing Neuroblasts," *iScience* 26 (2023): 107129.

102. A. Daeden, A. Mietke, and E. Derivery, "Polarized Branched Actin Modulates Cortical Mechanics to Produce Unequal-Size Daughters During Asymmetric Division," *Nature Cell Biology* 25 (2023): 235–245.

103. T. Kiyomitsu and S. Boerner, "The Nuclear Mitotic Apparatus (NuMA) Protein: A Key Player for Nuclear Formation, Spindle Assembly, and Spindle Positioning Front," *Frontiers in Cell and Developmental Biology* 9 (2021): 653801.

104. R. G. Fehon, A. I. McClatchey, and A. Bretscher, "Organizing the Cell Cortex: The Role of ERM Proteins," *Nature Reviews Molecular Cell Biology* 11 (2010): 276–287.

105. L. Balasubramaniam, R. M. Mège, and B. Ladoux, "Active Nematics Across Scales From Cytoskeleton Organization to Tissue Morphogenesis," *Current Opinion in Genetics & Development* 73 (2022): 101897.

106. A. L. Le Roux, C. Tozzi, N. Walani, et al., "Dynamic Mechanochemical Feedback Between Curved Membranes and BAR Protein Self-Organization," *Nature Communications* 12 (2021): 6550.

107. C. Tozzi, N. Walani, A. L. Le Roux, and P. Roca-Cusachs, "A Theory of Ordering of Elongated and Curved Proteins on Membranes Driven by Density and Curvature," *Soft Matter* 17 (2021): 3367–3379.

108. N. Ramakrishnan, R. P. Bradley, R. W. Tourdot, and R. Radhakrishnan, "Biophysics of Membrane Curvature Remodeling at Molecular and Mesoscopic Lengthscales," *Journal of Physics: Condensed Matter* 30 (2018): 273001.

109. Z. Wu, M. Su, C. Tong, M. Wu, and J. Lu, "Membrane Shape-Mediated Wave Propagation of Cortical Protein Dynamics," *Nature Communications* 9 (2018): 136.

110. O. Brandman and T. Meyer, "Feedback Loops Shape Cellular Signals in Space and Time," *Science* 322 (2008): 390–395.

111. Q. Yang, Y. Miao, P. Banerjee, et al., "Nanotopography Modulates Intracellular Excitable Systems Through Cytoskeleton Actuation," Proceedings of the National Academy of Sciences of the United States of America*U S A* 120 (2023): 2218906120.

112. Y. Shin and C. P. Brangwynne, "Liquid Phase Condensation in Cell Physiology and Disease," *Science* 357 (2017): aaf4382.

113. L. Baldauf, F. Frey, M. Arribas Perez, et al., "Branched Actin Cortices Reconstituted in Vesicles Sense Membrane Curvature," *Biophysical Journal* 122 (2023): 2311–2324.

114. G. Rivas and A. P. Minton, "Surfaces as Frameworks for Intracellular Organization," *Trends in Biochemical Sciences* 49 (2024): 942–954.

115. W. Y. C. Huang, S. G. Boxer, and J. E. Ferrell, "Membrane Localization Accelerates Association Under Conditions Relevant to Cellular Signaling," Proceedings of the National Academy of Sciences of the United States of America*U S A* 121 (2024): 2319491121.

116. A. M. Sokac, "Seeing a Coastline Paradox in Membrane Reservoirs," *Developmental Cell* 43 (2017): 541–542.

117. A. Gesper, S. Wennmalm, P. Hagemann, S. G. Eriksson, P. Happel, and I. Parmryd, "Variations in Plasma Membrane Topography can Explain Heterogenous Diffusion Coefficients Obtained by Fluorescence Correlation Spectroscopy," *Frontiers in Cell and Developmental Biology* 8 (2020): 767.

118. J. Adler, K. Bernhem, and I. Parmryd, "Membrane Topography and the Overestimation of Protein Clustering in Single Molecule Localisation Microscopy—Identification and Correction," *Communications Biology* 7 (2024): 791.

119. M. Bonucci, T. Shu, and L. J. Holt, "How It Feels in a Cell," *Trends in Cell Biology* 33 (2023): 924–938.

120. D. Liu, M. Riggi, L. HO, et al., "Depicting a Cellular Space Occupied by Condensates," *Molecular Biology of the Cell* 34 (2023): tp2.

121. B. Gouveia, Y. Kim, J. W. Shaevitz, et al., "Capillary Forces Generated by Biomolecular Condensates," *Nature* 609 (2022): 255–264.

122. L. Heinrich, D. Bennett, D. Ackerman, et al., "Whole-Cell Organelle Segmentation in Volume Electron Microscopy," *Nature* 599 (2021): 141–146.