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Review

Excitable networks controlling cell migration during development and disease

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ABSTRACT

The directed movements of individual, groups, or sheets of cells at specific times in particular locations bring about form and complexity to developing organisms. Cells move by extending protrusions, such as macropinosomes, pseudopods, lamellipods, filopods, or blebs. Although many of the cytoskeletal components within these structures are known, less is known about the mechanisms that determine their location, number, and characteristics. Recent evidence suggests that control may be exerted by a signal transduction excitable network whose components and activities, including Ras, PI3K, TorC2, and phosphoinositides, self-organize on the plasma membrane and propagate in waves. The waves drive the various types of protrusions, which in turn, determine the modes of cell migration. Acute perturbations at specific points in the network produce abrupt shifts in protrusion type, including transitions from pseudopods to filopods or lamellipods. These observations have also contributed to a delineation of the signal transduction network, including candidate fast positive and delayed negative feedback loops. The network contains many oncogenes and tumor suppressors, and other molecules which have recently been implicated in developmental and metabolic abnormalities. Thus, the concept of signal transduction network excitability in cell migration can be used to understand disease states and morphological changes occurring in development.

1. Introduction

Throughout phylogeny, migrating cells possess an internal compass which enables them to sense and move towards or away from gradients of extracellular, soluble chemoattractants or repellants, respectively. In-depth studies over the past century have revealed that chemotaxis plays a crucial role in the development and physiology of uni- and multicellular organisms. In bacteria, archaea and protozoa, cells perform chemotaxis for the purposes of seeking nutrients in the environment, intercellular aggregation and multicellular morphogenesis, and spreading infection within the host [1–4]. Apart from chemotaxis, cells possess the ability to sense and move along gradients of other environmental stimuli, such as light, electric fields, surface stiffness, shear forces, temperature, and substrate-bound signaling molecules [5–16].

In metazoans, directed cell migration is required during embryonic development and in adults. During embryogenesis, concerted movement of epithelial sheets bring about gastrulation, while precursor cells residing in different stem cell regions, such as neural crest, brain ventricles, somites and primitive streak, leave their niche and move towards their target sites [17–22]. In adults, guided migration is critical for several processes such as trafficking of immune cells towards invading pathogens, coordinated movement of keratinocytes and fibroblasts into the wound site during its healing, motility of sperm towards the egg during fertilization, homing of endogenous stem cells to maintain tissue homeostasis [23–28].

Irregularities in directional migration gives rise to congenital abnormalities, such as neuronal migration disorders, and inflammatory diseases, such as various allergies and infections, atherosclerosis, angiogenesis and cancer metastasis [29–34]. This review aims to summarize recent models and molecular mechanisms controlling individual cell migration. The concepts outlined here also shed light on understanding collective cell migration in development and diseases.

2. Varied cellular protrusions in a vast range of physiological functions

Migratory cells move with the help of a diverse array of morphological appendages, which lead to different migration modes. Bacteria, protozoa and sperm rely on flagella and cilia for propulsion and movement [1,35]. Leukocytes and amoebae move by rhythmically

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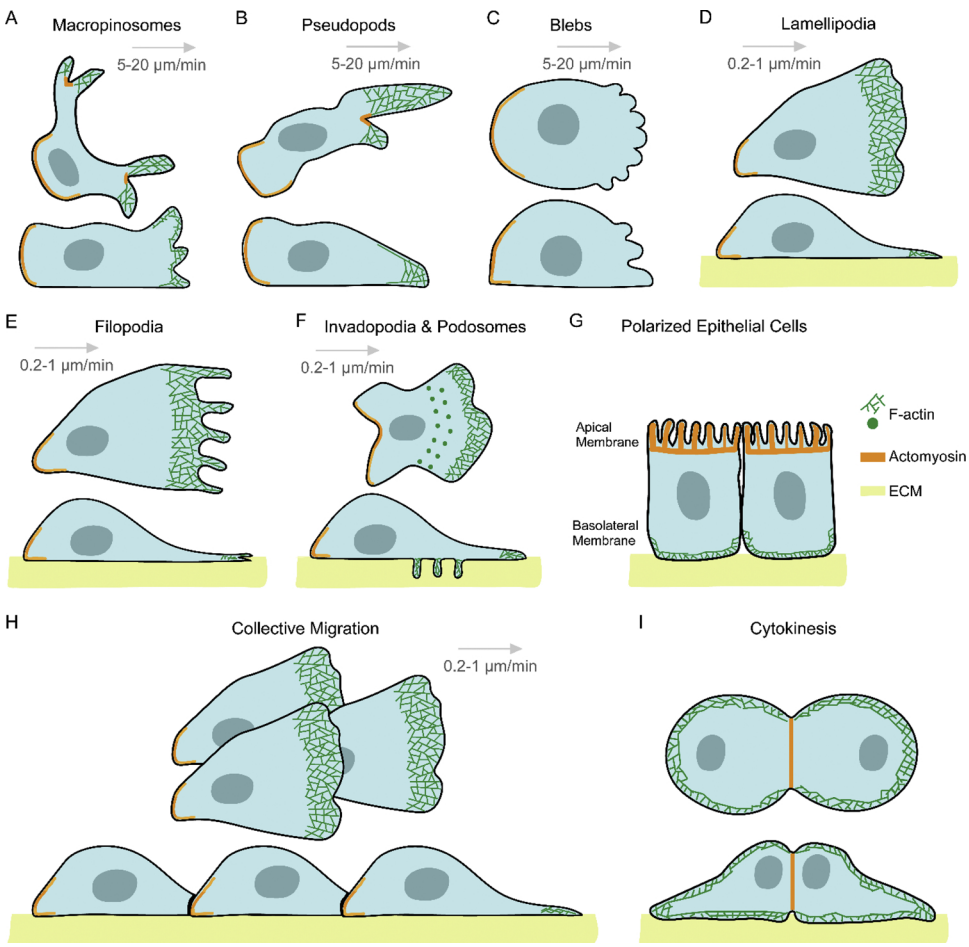


Fig. 1. Snapshots of diverse cellular protrusions in a variety of physiological functions. Throughout the illustration, all cells and their protrusions are shown in top (upper) and side (lower) views, except for polarized epithelial cells (G), which is shown only in side view. F-actin is denoted as mesh of green lines, actomyosin as a heavy orange line, and the extracellular matrix (ECM) is shown in yellow. For migratory cells, the direction of migration is from left to right, as shown with a grey arrow. The respective migratory speeds are mentioned below each grey arrow. Wide and cup-shaped macropinosomes (A) or narrower and longer pseudopods (B) are F-actin rich structures which extend and retract rhythmically near the top and sides of the amoeboid cell, or near the substratum, respectively. (C) In some instances, cells move with the help of bulky cytoplasmic structures or 'blebs' which form by detachment of cell membrane from the actomyosin cortex due to contractile pressure. Cells move at a fast speed of 5-20 μm/min with the help of macropinosomes, pseudopods or blebs. (D) Fibroblasts move on the ECM with the help of a broad, thin, F-actin filled anterior protrusion called lamellipodia. The actin network of these structures sometimes protrudes further to form thin, finger-like projections called filopodia (E). Due to the focal adhesion-based attachment of these cells to the ECM, they move at a far slower speed of 0.2-1 μm/min. (F) Macrophages and some cancer cells form polymerized actin-rich ventral protrusions, referred to as podosomes or invadopodia, which also secrete metalloproteases to degrade the ECM. (G) Epithelial cells polarize along the apical-basal axis and migrate very slowly as epithelial sheets. (H) During oogenesis and embryogenesis, actin polymerization directly pushes forward the plasma membrane of *Drosophila* border cells and Xenopus neural crest cells in the form of a broad lamellipodia, and help the cells to migrate collectively. (I) During cytokinesis, F-actin and actomyosin localize to the poles and cleavage furrow, giving the dividing cell the appearance of two cells migrating away from each other.

extending and retracting discrete actin-rich protrusions, which may appear as wide cup-like structures at the top and sides of the cell or narrower ones situated closer to the substratum. These are traditionally referred to as macropinosomes or pseudopods, respectively (Fig. 1A and B) [36–39]. In certain cases of amoeboid motion, due to contractile pressure, the plasma membrane detaches from the actomyosin cortex and causes cytoplasmic extensions or 'blebs' to appear (Fig. 1C) [20,40–42]. Keratocytes glide with the help of a single, broad, actin-filled, anterior protrusion and can preserve their shape and direction during motion [43,44]. Mesenchymal cells, such as fibroblasts, move on the extracellular matrix (ECM) with the help of sheet-like lamellipodia and thin, finger-like filopodia, which form at the leading edge of the cell (Fig. 1D and E) [45,46]. The attachment to the ECM causes these cells to move at a speed of 0.2-1 μm/min, while cells displaying amoeboid or keratocyte-like migration move at a speed of 5-20 μm/min [47].

Under different physiological conditions, variations of this general scheme can give rise to a diversity of protrusions and migration modes in cells. 1) Blood cells of myeloid and monocytic lineages or metastatic cancer cells form actin-rich ventral projections called podosomes or invadopodia, respectively, which degrade the ECM through secretion of matrix metalloproteinases, and help cells migrate across extracellular barriers (Fig. 1F) [48]. Interestingly, in patients suffering from Wiskott–Aldrich syndrome, dendritic cells and macrophages have defective podosome formation [49]. 2) Polarized epithelial cells display actomyosin enriched apical regions with broad, F-actin rich lamella-like protrusions at the baso-lateral surface. Their migration is limited due to intercellular interactions (Fig. 1G) [50,51]. 3) During oogenesis and embryogenesis, cells move collectively, including *Drosophila* border cell clusters, which detach from the follicular epithelium and migrate toward the oocyte [52,53]; *Drosophila* tracheal cell clusters, which branch out to form the tracheal system [54] and zebrafish lateral line primordium, which migrates to form the lateral line sensory system (Fig. 1H) [55]. 4) Though not technically cell migration, the process of cytokinesis resembles two cells migrating away from each other. Consistently, F-actin rich protrusions and myosin, which segregate to the anterior or posterior regions of migrating cells move to the poles or furrow of dividing cells during cytokinesis (Fig. 1I) [56,57]. Thus, varied actin-dependent protrusions are crucial for a vast range of cellular functions, including morphogenesis, tissue regeneration, immunity and cell division.

3. Spatiotemporal regulation of signal transduction and cytoskeletal networks

In migrating cells, many of the signaling molecules, including both lipids and proteins, that mediate polarity and directed cell migration are selectively localized or activated at the leading edge. While others, initially present on the membrane/cortex dissociate from the protrusions. These asymmetrically distributed molecules are referred to as "front" or "back", respectively. A growing list of such spatially restricted molecules is shown in Fig. 2A. For example, front events such as Ras, TORC2, PI3K activation, PKB localization or PIP3 accumulation occur at the tips of protrusions of the vegetative and polarized cells, and back events such as PTEN or Myosin II dissociation from pseudopods

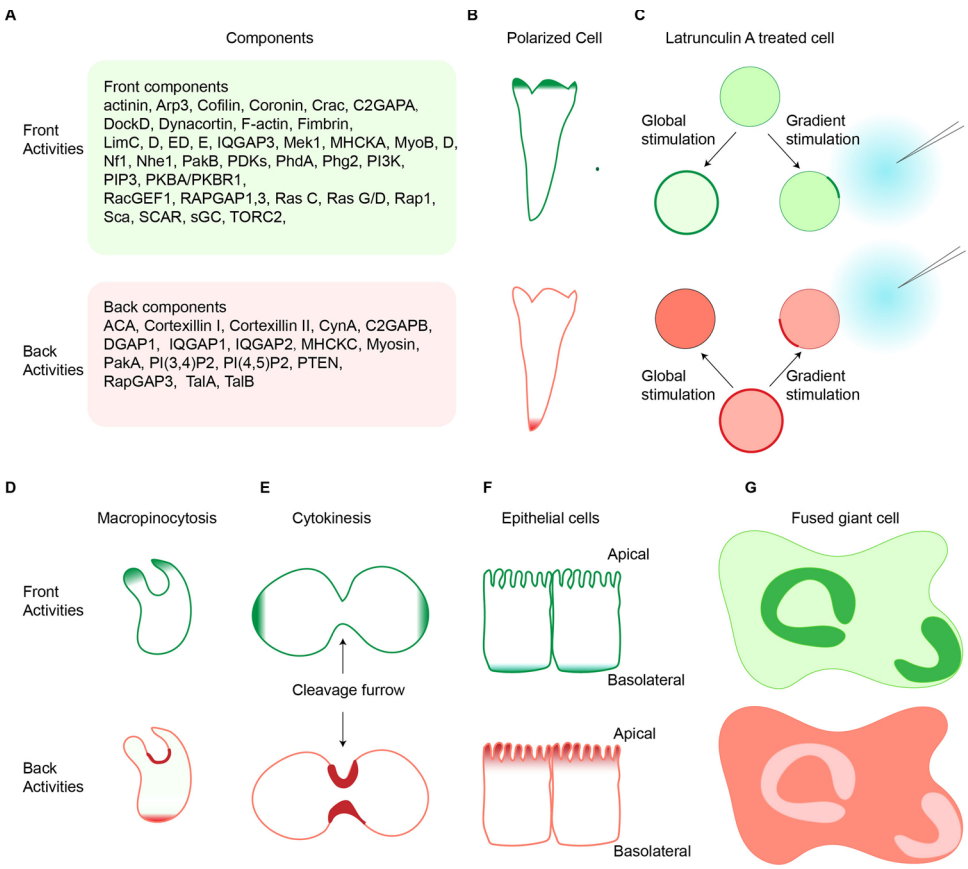


Fig. 2. Complementary front and back cellular events. A. Components of front (up) and back (bottom) are listed. (B). Front activities, such as Ras or PI3K activation, occur at the protrusions of migrating polarized cells, respectively (denoted in dark green, top row). These front activities are complemented with back activities, which localize to the trailing edge of the cells (denoted in red, top row). (C). Upon global or gradient chemoattractant stimulation, latrunculin A-treated cells also show opposite distribution of front (top) and back (bottom) activities. (D). During macropinocytosis, front activities is at the macropinocytic cup, and back activities are at the back of the cup and cell. (E). During cytokinesis, these front molecules are found at the poles of the dividing cells and the back molecules accumulate at the cleavage furrow. (F). In epithelial cells, the front events are localized to the basolateral surfaces (green, top), and the back events are at the apical side (red, bottom). (G). This complimentary pattern of front and back molecules is conserved in fused *Dictyostelium* cells.

and localization to the tail of the cells [58–65]. We use the terms "events" or "activities" throughout the review to refer to localization/accumulation or activation/deactivation of components. These complementary distributions of molecules and activities are a crucial first step in establishing polarity and guiding cell migration and are maintained even in the absence of a chemoattractant gradient (Fig. 2B). The same complementary pattern of front and back events is observed even when the actin skeleton is disrupted by Latrunculin A. As shown in Fig. 2C, in Latrunculin A-treated cells, front components such as PI3K are localized in the cytosol and back components like PTEN are on the membrane. In response to uniform chemoattractant, front components redistribute evenly over the cortex or membrane, whereas back components translocate into the cytosol. When the cells are exposed to a gradient of chemoattractant, front events show an accumulation in a 'dancing crescent' whose orientation oscillates around the direction of the gradient. The behavior of the back events such as PI(3,4)P2 accumulation is diametrically opposed and faces away from the gradient [66,67] (Fig. 2C).

There are situations which parallel migration where these complementary distributions are conserved. For example, during macropinocytosis, the extending edges of the forming cups are decorated with front components like PIP3, whereas back components like PTEN localize to the base (Fig. 2D) [68]. During cytokinesis, back components move uniformly to the membrane, while front components localized to the cytosol. As the cell elongates, front proteins associate with the cell membrane at the poles while back proteins accumulate at the cleavage furrow together with the acto-myosin ring (Fig. 2E) [69]. In epithelial cells, front events are localized to the basolateral surfaces, and back events are at the apical side [70] (Fig. 2F). In multinucleated mutants or fused giant *Dictyostelium* cells, which display waves of actin polymerization, the same complementary patterns of front and back events are again observed as shown in Fig. 2G [71]. Most of the basal surface is occupied by back markers, except in the region of actin polymerization where the front molecules appear.

We have observed that cytoskeletal activity alone produces only transient, narrow extensions. Upstream signal transduction networks are needed to provide coordination of cytoskeletal activities across protrusive cellular structures. When accompanied by signal transduction events, such as Ras and PI3K activation or PTEN inhibition, the protrusions are sustained, reaching out wider or longer [72]. The complementary distributions of these front and back events observed have an important role in regulating protrusions. In *Dictyostelium*, the coordinated activity of at least thirteen biosensors suggests that activation of the entire signal transduction network accompanies each protrusion. The molecular components involved in cell migration are remarkably conserved between the social amoeba, *Dictyostelium* and mammalian cells. *Dictyostelium* cells are easily cultivable in the laboratory, well suited for live cell imaging and are naturally migratory cells and have a haploid genome which is completely sequenced and annotated. This makes the amoeba an excellent model system for studies of eukaryotic cell migration [73–75].

Furthermore, as described below, small shifts in these upstream events can elicit a striking transition in different protrusive activities and migratory modes [58,76,77]. These observations are not accounted for in the classical view of cell migration. It is believed that different types of protrusions, such as filopodia and lamellipodia, are the results of activations of specific regulators of the actin-myosin cytoskeleton, such as Arp2/3 and formins [78–80], and signal transduction networks merely provide directionality to these protrusions. In the following sections, we discuss emerging insights into the role of spontaneous signal transduction events in the formation of the protrusions.

4. Excitability of signal transduction and cytoskeletal networks

Accumulating evidence points to the fact that these signal transduction and cytoskeletal activities are excitable. Excitability has served

as an emerging framework to decipher numerous biological systems, from neuronal action potentials to cardiac calcium waves, from yeast glycolytic oscillations to vertebrate segmentation. Excitable systems have characteristic hallmarks such as all-or-none response, refractoriness and wave propagation. Quantitative measurement in *Dictyostelium* has directly demonstrated the excitable nature of the signal transduction and cytoskeletal networks. For example, Huang et al. showed that activation of Ras, in response to short and long supra-threshold stimuli is the same and are followed by a refractory period of ˜50 seconds [81]. Consistently, signal transduction and cytoskeletal constituents propagate as waves on the cortex and annihilate when oppositely-directed waves collide, further supporting the existence of excitability (see Fig. 2E) [82,83]. With similar observations being described in other cell types including neutrophils [84–86], macrophages [87], and mast cells [88–90], excitability is likely a conserved feature of many molecular networks.

The signal transduction and cytoskeletal events appear to operate as distinct, yet closely interacting, excitable systems. In *Dictyostelium*, molecular events in cell migration can be broadly classified into two networks, the Signal Transduction Excitable Network (STEN) and the Cytoskeletal Excitable Network (CEN) (Fig. 3A). Differences between STEN and CEN are manifested in their responding kinetics to global stimulus, as well as localization morphologies in spontaneous wave patterns. In response to cAMP addition, STEN components, including phospholipids, Ras/Rap small GTPases, and PKBs, show a level/activity increase with kinetics slower than CEN components including F-actin, Rac, coronin, and HPSC300. Consistently, in spontaneous traveling waves, STEN components show diffuse bands while CEN display sharp 'two-peak' morphologies and puncta associated with the trailing peak (Fig. 3B). These differences in kinetics and localization highlight the intrinsic differences in excitability between STEN and CEN. On the other hand, STEN and CEN are closely coupled and entrained. Acute perturbations at different nodes suggest that STEN drives CEN to form waves. CEN also regulates the triggering of STEN, possibly through RapGAP1 and GflB [76,77]. Future work is required to reveal more detailed biochemical interactions and integrate them on a systematic level.

5. Wave patterns, cortical dynamics and cellular protrusions

The idea that wave propagation controls protrusion formation has been supported by recent evidence. It was found that fast undulations of CEN cover the cell periphery, but sustained protrusions are only formed when significant STEN activities drive CEN to support wave propagation [72,77,81,91]. Furthermore, the dynamic properties of wave propagation closely mirror those of pseudopods in migrating cells. Innately, waves of STEN and CEN have limited range – they gradually decrease speed and eventually extinguish rather than propagating persistently. Similarly, pseudopods only grow to a defined size before collapsing rather than expanding continually [36,92–94]. Thus, STEN and CEN waves, serving as the drivers of protrusions, can account for the extension and retraction dynamics of pseudopods.

Recent experiments with acute perturbations further support the causal relationship between wave properties and protrusion determination (Fig. 4). First, within minutes of lowering threshold of STEN activation, by decreasing PIP2 or increasing Ras/Rap activities using chemically induced dimerization, waves propagate with elevated speed and range. Consequently, narrower pseudopods become wider lamellipodia-like protrusions and the cell migratory mode shifts from amoeboid to keratocyte-like and oscillatory (Figs. 4B and F). Second, increasing PKBs activities produces negative feedback in STEN, but also promotes coupling between STEN and CEN. This raises the threshold of STEN, and simultaneously lowers threshold of CEN, leading to slower wave propagation and more wave initiation centers (Fig. 3A). This generates numerous spiky filopodia-like protrusions (Figs. 4C and G). Similarly, recruiting RacGEF1 to the membrane produces positive feedback in CEN, and delayed negative feedbacks in STEN. This lowers the threshold of CEN and increases threshold of STEN, leading to disrupted wave patterns and many diffuse actin patches (Fig. 3A). As a result, sustained protrusions cannot be formed due to a lack of wave propagation, and the cells generate ruffles on the cortex and lose the ability to move (Figs. 4D and H) [77]. All these transitions occur in a much faster time scale than that of gene regulation. Thus, tweaking the feedback loops within and between STEN and CEN leads to a range of wave patterns, which results in a spectrum of interchangeable cellular protrusions.

Future work is needed to advance the hypothesis that set points of the STEN-CEN machinery determine various types of cellular protrusions. Sophisticated higher resolution imaging is required to directly visualize and analyze wave propagation patterns at sites of different protrusions, given the challenges posed by the highly dynamic and three-dimensional nature of the cortex of migrating cells. Moreover, the extent to which this model is conserved must be tested. It is possible that different cells types have different expression levels of the STEN-CEN components innately, which holds the networks of each cell at a specific set point. Thus, different cells display specific types of protrusions predominantly. Finally, the connection between the wave properties and specific cytoskeleton nucleators needs investigation. It is interesting to note that blebs, usually thought to be controlled by hydrostatic pressure rather than any actin regulators, are nevertheless associated with Ras activation (Fig. 5), pointing to the possibility of using the STEN-CEN framework to fully comprehend bleb formation.

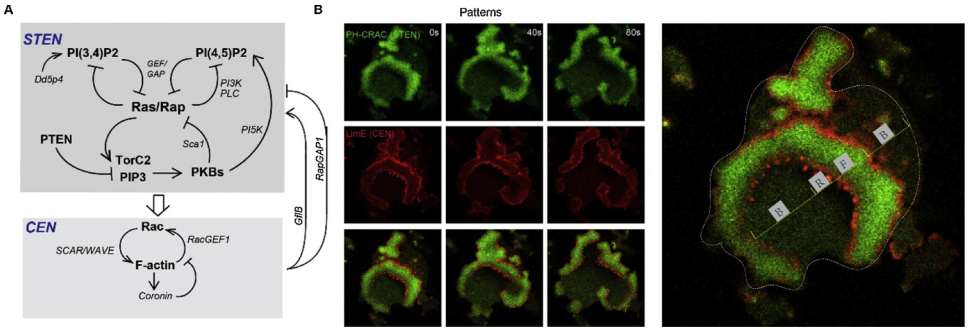


Fig. 3. Summary of STEN and CEN networks with positive and negative feedback loops. (A) Positive feedback in STEN is brought about by mutual inhibition between Ras/Rap activity and PI(3,4)P2 and PI(4,5)P2 at the cell cortex and delayed negative feedback due to PKB activation by PIP3 and TorC2. (B). The corresponding B, F, and R states are depicted on basal surface of a fused *Dictyostelium* cell. Time-lapse Confocal images (left) showing distribution of LimE (red) and PHcrac (green) during wave propagation at the basal surface of a migrating fused Dictyostelium cell. White dashed line marks the outline of the fused cell (Right). F represents the F state, B represents the B state and R represents the R state. The B-state region is characterized by low Rap/Ras, TorC2, and PI3K activity and high PI(3,4)P2 and PI(4,5)P2 levels. As a region transitions to the F-state, Rap/Ras activity increases, PI(3,4)P2 decreases strongly, and PI(4,5)P2 decreases slightly. There is a slower rise in PKB activity due to the elevation of TorC2 and PIP3. A refractory period (R state) follows associated with lower Rap/Ras activity and higher PI(3,4)P2/PI(4,5)P2 levels and PKB activity. The PKBs feed into CEN, promoting F-actin polymerization and loss of cortical myosin. In turn, the activated cytoskeletal activity provides fast positive and slow negative feedbacks to STEN.

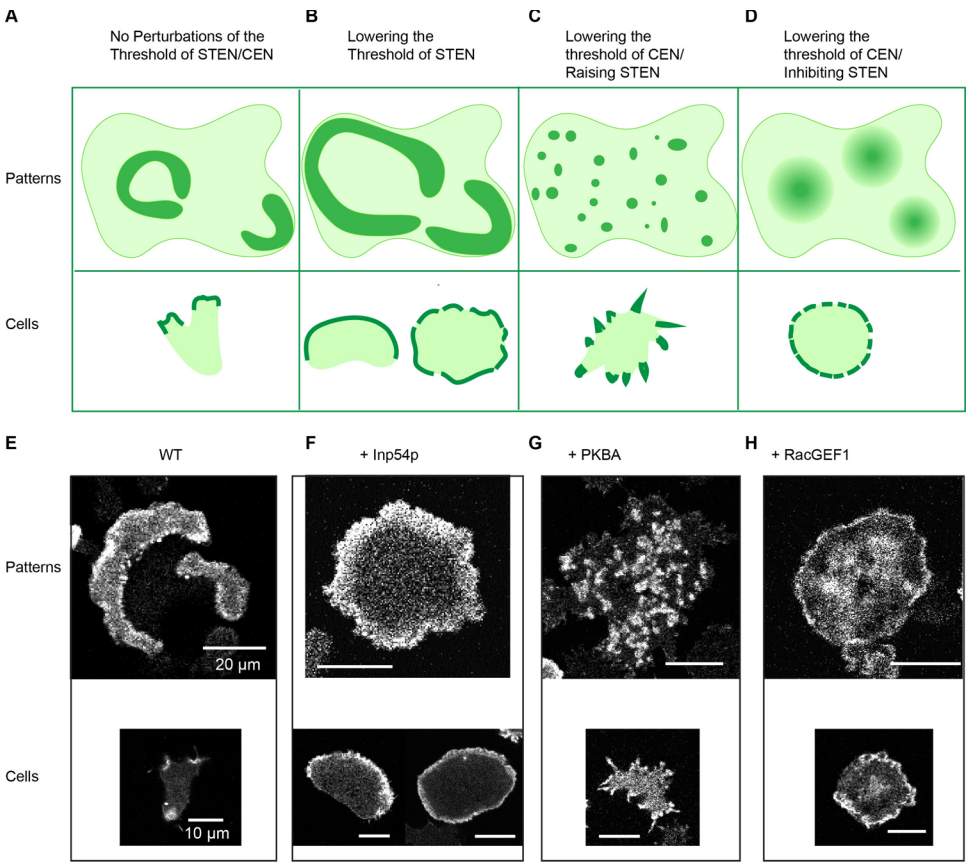


Fig. 4. Cartoon of Perturbations and different wave patterns & cellular protrusions.
(A-D). Cartoons depicting the cortical wave patterns corresponding to cellular morphology in fused giant cells (top) or single cells (bottom). Cells without perturbations of the threshold of STEN/CEN (A); with perturbations of lowering the threshold of STEN (B); with perturbations of lowering of the threshold for CEN/raising that of STEN (C); with perturbations of lowering of the threshold of CEN/removing STEN (D). (E-H) Confocal images corresponding to (A-D), showing LimE patterns (CEN) on the basal surface of fused *Dictyostelium* cells (top) and on the protrusions of single cells (bottom). Cells without perturbations of the threshold of STEN/CEN. (E); with perturbations of lowering PI(4,5)P2 by recruitment of 5-phosphatase Inp54p (lowers the threshold for STEN) (F); with perturbations of recruitment of PKBA (lowers the threshold of CEN and raises that of STEN) (G); with perturbations of recruiting RacGEF1 (lowers the threshold of CEN/extinguishes STEN) (H). Scale bar top 20 μm, bottom 10 μm.

6. Molecular mechanisms giving rise to excitability and wave patterns

Activator-inhibitor systems are typically used to explain wave propagation and excitability. In these systems, the activator is controlled by an autocatalytic loop, and generates the inhibitor, which provides negative feedback to the activator [95,96]. Further refinement of this model proposes that local regions of the cell cortex transition between inactive, active, and refractory states, designated as B, F, and R, respectively. Mutual inhibition between the B and F states creates the positive feedback loop. The F and R states are related through a delayed negative feedback loop. In resting cells, most of the cortex is in the B state. Once initiated, waves propagate outwardly because diffusion of F state components triggers activation in adjoining B but not R region

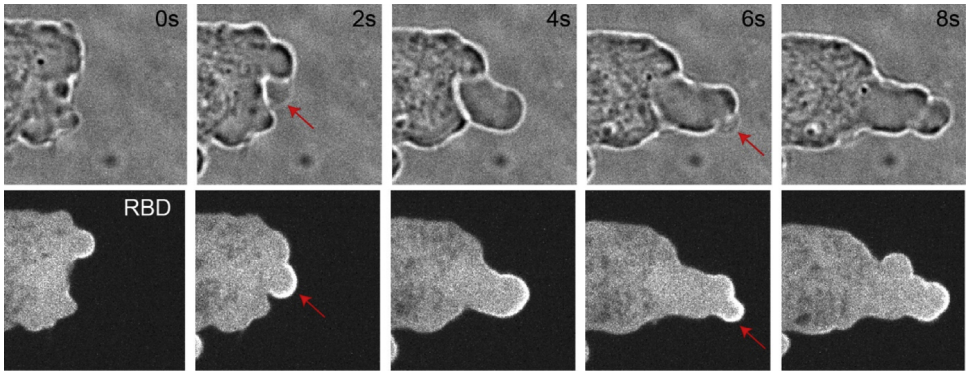


Fig. 5. Blebs are associated with Ras activation. The time-lapse confocal images of the same cell were obtained every 2 s. Confocal images showing blebs under bright field (top) and Ras activity sensor, Ras-binding domain of Raf-1 (RBD-GFP) under confinement in *a Dictyostelium* cell. Red arrows point to newly forming blebs.

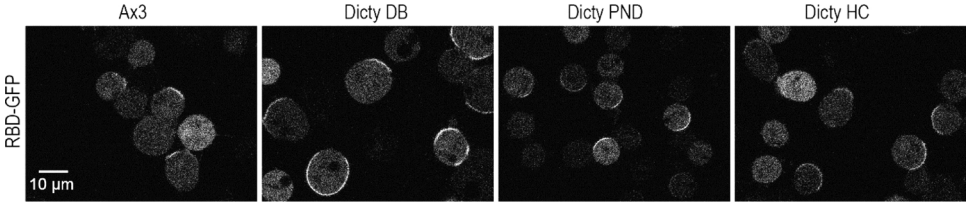
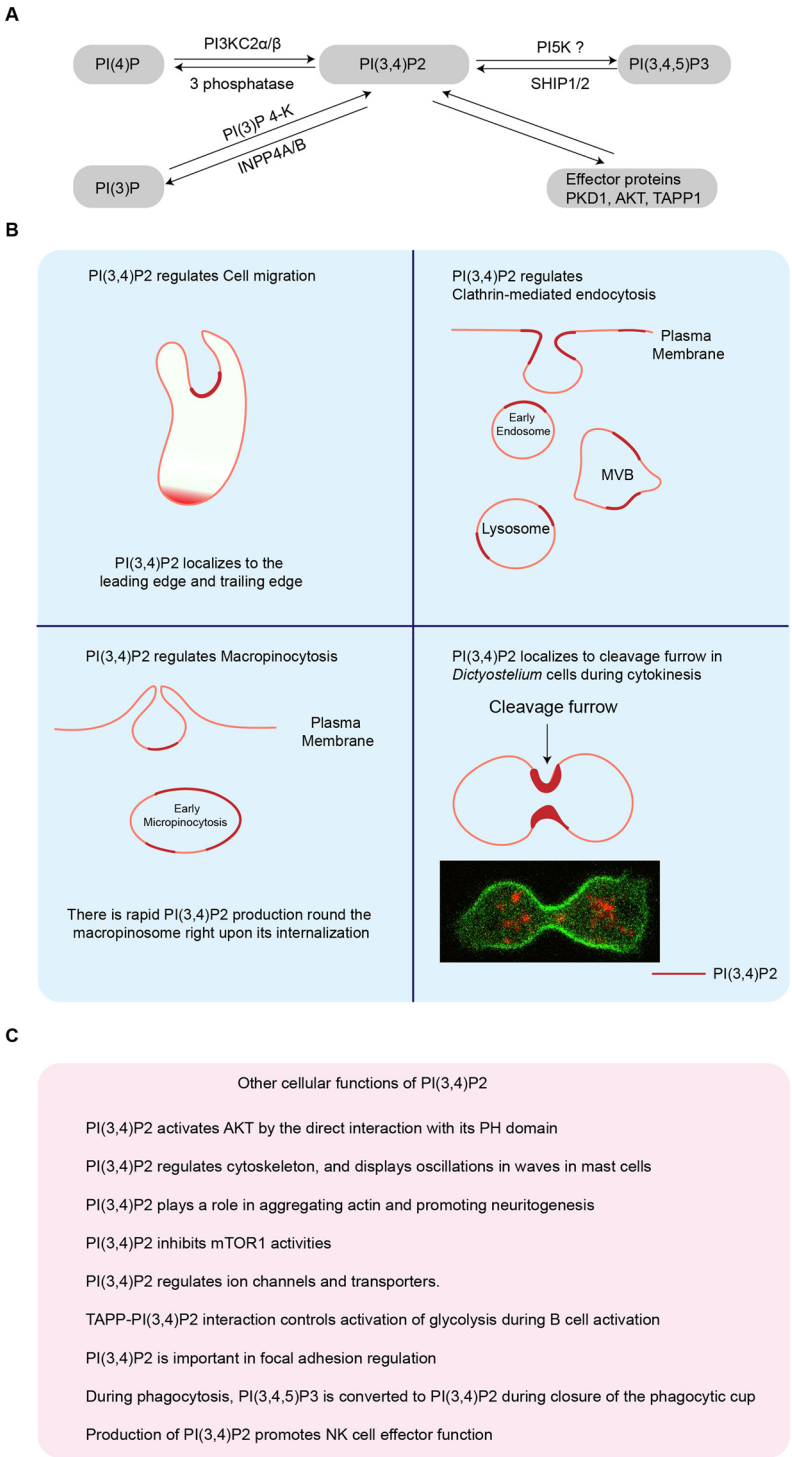


Fig. 6. RBD activities in wild-type Ax3 cells and in Dd5P4- cells. Confocal images showing RBD patches in wild-type Ax3 cells and three independently generated *Dd5P4-* cell lines. *Dd5P4-* cells from Dictybase stock center, *Dd5P4-* cells from Devreotes lab, Dd5P4- cells from Cai lab. Cells are treated with Latrunculin A for 20 min. Scale bar 10 μm.

Box 1
The cellular functions of PI(3,4)P2.



(A). PI(3,4)P2 metabolism pathways. (B). Dynamics, localization, and roles of PI(3,4)P2 during cell migration, endocytosis, macropinocytosis and cytokinesis [137–139]. PI(3,4)P2 localizes to the leading edge and lagging edge during cell migration [64,67,140,141]. PI(3,4)P2 localizes to the early endosome, multivesicular body (MVB), and lysosome during clathrin mediated endocytosis [142–145]. PI(3,4)P2 localizes to the back of the macropinocytic cups and early macropinosomes during micropinocytosis [144,146–150]. PI(3,4)P2 localizes to the cleavage furrow during cytokinesis (C). The other cellular functions of PI(3,4)P2 highlighted in pink box. PI(3,4)P2 activates AKT by the direct interaction with its PH domain [151]. PI(3,4)P2 regulates cytoskeleton, and displays oscillations in waves in mast cells [87,89,152,153]. PI(3,4)P2 plays a role in aggregating actin and promoting neuritogenesis [154]. PI(3,4)P2 inhibits mTOR1 activities [155]. PI(3,4)P2 regulates ion channels and transporters [156,157]. TAPP-PI(3,4)P2 interaction controls activation of glycolysis during B cell activation [158]. PI(3,4)P2 is important in focal adhesion regulation [159]. During phagocytosis, PI(3,4,5)P3 is converted to PI(3,4)P2 during closure of the phagocytic cup [160]. Production of PI(3,4)P2 promotes NK cell effector function [161].

[97]. Computational analyses based on such reaction–diffusion equations are able to simulate the distributions of F, B and R during wave propagation.

Mutually inhibitory interactions between Ras/Rap and PI(3,4)P2/ PI(4,5)P2 activities comprise a positive feedback loop, consistent with assigning these components as F and B, respectively. When cells are stimulated, Ras is activated, while PI(3,4)P2 levels drop significantly, and PI(4,5)P2 levels drop slightly. When PI(3,4)P2 levels are lowered with genetic or synthetic tools in the cells, Ras/Rap activities are elevated (Fig. 3A). Purified Lowe oculocerebrorenal syndrome protein (OCRL) homolog, Dd5P4, has been shown to generate PI(3,4)P2 from PI (3,4,5)P3 *in vitro,* and Li and Edwards et al have reported PI(3,4)P2 level is low in Dd5P4 null cells. An example is shown in Fig. 6, wild-type cells display one to three small patches of Ras activity, but the Dd5P4 null cells, which have lower PI(3,4)P2 levels, display higher Ras activities. Similarly, Miao et al found that acute lowering of PI(4,5)P2 levels promotes Ras/Rap activities. These regulations of Ras/Rap activities by PI(3,4)P2/ PI(4,5)P2 may occur through GEF and GAP proteins. In fact, Li and Edwards et al found that PI(3,4)P2 binds to and regulates RasGAP and RapGAP proteins [67,76]. These results add to the emerging role of PI(3,4)P2 in multiple cellular processes as elaborated in Box 1.

As positive feedback grows, negative feedback builds in a delayed manner. Charest et al. found that *Dictyostelium* cells lacking PKBA and PKBR1 display persistently high RasC activity in pull-down assays, suggesting a negative feedback loop involving the phosphorylation of upstream components by downstream PKBs [98–100]. Miao et al. showed that in immobilized cells lacking PKBs, RBD patches are more frequent but the patches are rapidly quenched by recruitment of PKBA [77]. These observations suggest that activation of PKBs serves as a negative feedback loop. Possible mechanisms may include inhibition of RasGEF, Aimless, and activation of PI5K to increase PI(4,5)P2 synthesis. Interestingly, PIP3 as an activator of PKBA, plays a negative role in STEN, while it is also an important positive regulator of actin polymerization. This may occur through a series of PKBA substrates (Fig. 3A).

Some other feedback loops have also been described. For example, a positive-feedback loop appears to link cytoskeletal events and PIP3 because inhibition of either reduces the spontaneous activation of the other [101,102]. There is other evidence that such a positive feedback path involving Ras exists [103]. It has been reported that the cortex of vertebrate and invertebrate oocytes and embryos is also an excitable medium. Positive feedback is mediated by Rho autoactivation and negative feedback is mediated by F-actin-mediated Rho inhibition [104]. Taken together, these suggest that individual molecular regulators of various protrusions are feeding into the same overall molecular machinery. Global properties and feedback loops of the Ras/Rap-centered STEN and Rac/F-actin centered CEN are the true determinants of controlling the entire spectrum of protrusions observed in cell migration.

7. Dysregulations of signaling events in development and disease

We suggest that a variety of diseases involving altered cell migration or morphology may be viewed as changes in the set point of the excitable networks. Many of the signaling molecules involved in the feedback loops are often mutated or deleted in a variety of cancers (Fig. 3A). Examples include PIK3CA (p110a) is mutated in a range of tumors [105], PTEN is a well-established tumor suppressor in a large proportion of human cancers [106], some 5-phosphatases such as SHIP2 and PIB5PA and the 4-phosphatase INPP4B act as tumor suppressors in various cancers [107–110], Myosin II is reported to be involved in cancers and regional activation of Myosin II in amoeboid cancer cells drives tumor progression [111–114]. Of course, Ras is a ubiquitous oncogene, with activating mutations in kRas, nRas, or hRas found in 27% of all human cancers [115]. Finally, Rho GTPases are altered in multiple different cancers as well as melanoma [116]. As we have observed in *Dictyostelium* and cultured mammalian cells, loss or gain of function in these oncogenes and tumor suppressors *in vivo* likely leads to alterations of the threshold of excitable networks, and consequently, the morphological changes typically associated with cancer cells.

These signaling molecules are also involved in other human diseases, which might also be traced to effects on excitable networks. PTEN is implicated in a subset of autism and Alzheimer's disease [117,118]. Mutations in SHIP2 are associated with Type II diabetes [119,120], hypertension [121] and Alzheimer's disease [122]. PTEN or SHIP1 deletions in neutrophils show increased motility and excessive recruitment to inflamed sites [64,123]. Mutations in the PI 5-phosphatase, INPP5E, are causative of MORM syndrome [124]. Mutations in the genes encoding erythroid membrane skeletal proteins lead to hereditary haemolytic anaemias [125]. The mechanisms responsible for the pathophysiology of Wiskott–Aldrich syndrome (WAS) are directly linked to lack of Wiskott–Aldrich syndrome protein (WASP) and deficient actin organization in haematopoietic cells [126].

Cell migration is extensively employed during development to form the embryo. Defects in migration often result in central nervous system malformations [127–130]. Autism Spectrum Disorder (ASD) is associated with changes in the morphology of dendritic spines [131]. Moreover, several syndromes such as Waardenburg, Carpenter, Alagille and CHARGE, have been traced to impaired migration of neural crest cells, resulting in deafness, pigmentation changes, abnormalities of the bones of skull and digits, defective heart, liver and genitals, and growth retardation in adults [132–136].

8. Conclusions

The excitable network hypothesis for cell migration may provide a novel framework for understanding morphological changes in cells. In this review, we explained how waves of signal transduction activities drive various types of protrusions, which in turn, determine the modes of cell migration. Going forward, it will be important to determine the extent to which the same or similar excitable networks are used in migrating cells in developing embryos as have been elaborated for *Dictyostelium* and several mammalian cells lines.

Author contributions

X.L and Y.M. contributed experimental data; X.L., Y.M., D.S.P. and P.N.D. wrote the manuscript. D.S.P. made Fig. 1; X.L. prepared Figs. 2–6 and Box 1; Y.M. prepared Figs. 3A and 5 .

Declaration of Competing Interest

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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