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The Excitable Signal Transduction Networks: Movers and Shapers of Eukaryotic Cell Migration

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Abstract

In response to a variety of external cues, eukaryotic cells display varied migratory modes to perform their physiological functions during development and in the adult. Aberrations in cell migration results in embryonic defects and cancer metastasis. The molecular components involved in cell migration are remarkably conserved between the social amoeba, *Dictyostelium* and mammalian cells. This makes the amoeba an excellent model system for studies of eukaryotic cell migration. These migration-associated components can be grouped into three networks- input, signal transduction and cytoskeletal. In migrating cells, signal transduction events such as Ras or PI3K activity occur at the protrusions tips, referred to as ‘front’, whereas events such as dissociation of PTEN from these regions are referred to as ‘back’. Asymmetric distribution of such front and back events is crucial for establishing polarity and guiding cell migration. The triggering of these signaling events displays properties of biochemical excitability including all-or-nothing responsiveness to suprathreshold stimuli, refractoriness, and wave propagation. These signal transduction waves originate from a point and propagate towards the edge of the cell, thereby driving cytoskeletal activity and cellular protrusions. Any change in the threshold for network activation alters the range of the propagating waves and the size of cellular protrusions which gives rise to various migratory modes in cells. Thus, this review highlights excitable signal transduction networks as key players for coordinating cytoskeletal activities to drive cell migration in all eukaryotes.

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AUTHOR CONTRIBUTIONS

D.S.P., T.B. and Y.M. contributed experimental data; D.S.P., X.L. and P.N.D. wrote the manuscript; T.B. conceptualized figure 2, X.L. prepared figures 1, 2, 4 and 5, and D.S.P. made figure 3; D.S.P., X.L., T.B., Y.M. and P.N.D. contributed to manuscript revision and approved the submitted version of the manuscript.

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Dictyostelium; macrophage; migration; signal transduction; excitability; protrusion

Dictyostelium paves the way for understanding cell migration in human health and disease

In eukaryotic cells, cell migration is crucial for a multitude of physiological processes. During embryogenesis, migration of individual or groups of cells, in response to external cues, leads to formation of various glands and organs, and wiring of the nervous system (Montell 2008). Examples include the coordinated movement of epithelial cell sheets at the onset of gastrulation and neurulation (Yang, Dormann et al. 2002, Keller 2005, Leptin 2005, Theveneau and Mayor 2012), movement of primordial germ cells across the embryo towards the developing somatic gonads (Blaser, Reichman-Fried et al. 2006, Richardson and Lehmann 2010) or glial and neural precursor cell migration in the central and peripheral nervous systems (Klambt 2009). In adults, directed migration is observed during host inflammatory responses when immune cells move through tissues and vessels towards invading pathogens (Nourshargh and Alon 2014, Weninger, Biro et al. 2014), or various cellular regenerative processes such as wound healing performed by concerted movement of fibroblasts and keratinocytes (Shaw and Martin 2009). Cells are able to sense and integrate a variety of external cues from the environment and each other, including chemicals (Tessier-Lavigne 1994, Bagorda and Parent 2008), electric fields (Zhao, Song et al. 2006, Gao, Zhang et al. 2011, Cortese, Palama et al. 2014), light (Armitage and Hellingwerf 2003), temperature (Whitaker and Poff 1980, Ramot, MacInnis et al. 2008) and mechanical forces (Lo, Wang et al. 2000, Harland, Walcott et al. 2011). Irregularities or defects in cell migration are responsible for pathogenesis of several inflammatory diseases such as acute respiratory distress syndrome, several allergies (asthma, allergic rhinitis and atopic dermatitis), arthritis, atherosclerosis, periodontal disease, sarcoidosis and Wiskott-Aldrich syndrome (Lakshman and Finn 2001, Moulding, Record et al. 2013). Cell migration is also a crucial phenomenon during cancer metastasis when tumor cells detach and spread from their primary site of origin to colonize other tissues and organs of the body (Kedrin, van Rheenen et al. 2007).

Eukaryotic cells perform their crucial physiological functions by displaying a variety of migratory behaviors. Migration in these cells is achieved by coordinated extension of actin-rich protrusions at the leading edge of the cell, and actomyosin filaments-based contraction at the trailing edge. (Figure 1A). Variations of this cytoskeletal organization in the cell give rise to a vast repertoire of migratory behaviors. Leukocytes, hematopoietic stem cells and several metastatic cancer cells translocate by amoeboid motility, a rhythmic extension and retraction of actin-filled pseudopodia leading to cell movement in random directions. Primordial germ cells use an unusual type of amoeboid motion, termed as blebbing, which involves extension of rounded cytoplasmic bulges caused by detachment of plasma membrane from actomyosin cortex due to myosin-based contraction (Blaser, Reichman-Fried et al. 2006, Yoshida and Soldati 2006, Fackler and Grosse 2008). Keratocyte-like migration, seen in mesenchymal-derived corneal stromal cells, is characterized by large,

actin-driven, fan-like lamellipodia at the front and sides of the cell causing them to move in a rolling motion (Barnhart, Allen et al. 2010). This mechanism leads to the fastest motion and cells can maintain constant direction and speed over several cell lengths (Anderson and Cross 2000). “Mesenchymal” migration, seen in fibroblasts, is much slower than amoeboid or keratocyte-like motility and is mediated by lamellipodia at the leading edge of the cell (Hou, Hedberg et al. 2012). This type of migration depends on focal adhesions between cell and extracellular matrix whereas amoeboid or keratocyte migration involves more transient attachment of cells to the substratum (Mogilner and Keren 2009, Parsons, Horwitz et al. 2010). In this review, the focus primarily would be on understanding the signal transduction events in amoeboid migration in cells, although it is explained how cells can abruptly switch between migratory modes.

Most of the present-day knowledge regarding amoeboid-type migration in eukaryotic cells was first revealed from seminal studies in the social amoeba, *Dictyostelium*. For example, identification of actin binding proteins such as coronin (de Hostos, Bradtke et al. 1991), functional redundancy of cytoskeletal components involved in cell migration (Andre, Brink et al. 1989, Witke, Schleicher et al. 1992, Jung, Wu et al. 1996), role of myosin II in cytokinesis and cell migration (De Lozanne and Spudich 1987, Wessels, Soll et al. 1988), identification of chemoattractant receptors as GPCRs (Klein, Sun et al. 1988), confinement of phosphoinositide lipids and G protein signaling events to the leading edge of migrating cells (Parent, Blacklock et al. 1998, Iijima and Devreotes 2002), involvement of Ras GTPases in cell migration (Insall, Borleis et al. 1996, Kae, Lim et al. 2004, Sasaki, Janetopoulos et al. 2007), and discovery of actin waves (Vicker 2002). Due to evolutionary conservation between *Dictyostelium* and higher eukaryotes, these scientific discoveries paved the way for understanding the role of migration-associated signal transduction and cytoskeletal networks in human physiology and pathology (Parent 2004, Bagorda, Mihaylov et al. 2006).

The amenability of *Dictyostelium* to experimentation enabled these discoveries. It is easily cultivable in the laboratory, and is well suited for live cell imaging. It has a haploid genome which is completely sequenced and annotated, thereby facilitating genetic manipulations (Muller-Taubenberger, Kortholt et al. 2013). Moreover, *Dictyostelium* are naturally migratory cells which respond to chemoattractants such as 3’, 5’-cyclic adenosine monophosphate (cAMP) as part of their development program, and folic acid to seek nutrients (Chisholm and Firtel 2004, Mahadeo and Parent 2006). These processes can be mimicked in the laboratory with relative ease which makes the amoeba the premier model system for investigating cell migration.

Spatiotemporal control of signal transduction networks regulates cell migration

The components involved in cell migration can be grouped into input, signal transduction, and cytoskeletal networks, which show functional conservation between *Dictyostelium* and mammalian cells (Figure 1B). Chemical, electrical or mechanical stimuli locally activate the signal transduction networks through input networks which consists of different receptors or

sensors (Zhao, Jin et al. 2002, Zhao, Song et al. 2006, Meng, Arocena et al. 2011, Allen, Mogilner et al. 2013, Miao, Bhattacharya et al. 2017). In *Dictyostelium*, the input network is comprised of cAMP and folic acid GPCRs (cARs and FARs respectively) along with associated G proteins (Gα2, Gα4, Gα9 and Gβγ) (Klein, Sun et al. 1988, Wu and Devreotes 1991, Parent and Devreotes 1996, Kimmel and Parent 2003, Pan, Xu et al. 2016). The input network of mammalian cells consists of GPCRs and associated G proteins (Gαi, G12α, G13α and Gβγ), RTKs, integrins and chemokine receptors (Figure 1B) (Baggiolini 2001, Manes, Gomez-Mouton et al. 2005, Stephens, Milne et al. 2008, Senoo, Sesaki et al. 2016). Chemokine receptors have been found to be functionally similar to cARs and FARs in *Dictyostelium* (Jin, Xu et al. 2008). These sensors detect gradients of chemoattractants (cAMP and folic acid for *Dictyostelium* or chemokines, cytokines and growth factors for mammalian cells) in the environment, thereby triggering downstream signal transduction components and enabling the cell to migrate along the gradient.

The signal transduction network is comprised of components which are arranged in several interconnected or parallel pathways. In *Dictyostelium*, it consists of various molecules including Ras proteins (RasG, RasD and RasC), phosphoinositide lipids [phosphatidylinositol (3,4,5)-trisphosphate or PIP3, phosphatidylinositol 3,4-bisphosphate or PI(3,4)P2 and phosphatidylinositol 4,5-bisphosphate or PI(4,5)P2], and several kinases and phosphatases (PI3K, PTEN, Dd5P4 and PKBA/PKBR1). The signaling network in mammalian cells is analogous including H-Ras, K-Ras, PIP3, PI(3,4)P2, PI(4,5)P2, PI3K, PTEN, SHIP and Akt (Figure 1B) (Wilkins and Insall 2001, Tang, Iijima et al. 2011, Devreotes and Horwitz 2015, Devreotes, Bhattacharya et al. 2017, Simanshu, Nissley et al. 2017). Studies suggest that the role of the Ras-PIP3 network in mammalian cell migration is remarkably consistent with that in *Dictyostelium* (Artemenko, Lampert et al. 2014). Other reports have shown that interactions between Ras/Rap1 family proteins and TorC2 are conserved and thereby coordinate migration in *Dictyostelium* and mammalian cells (Charest, Shen et al. 2010, Khanna, Lotfi et al. 2016). Importantly, these network events are spontaneously activated leading to cell migration even in absence of an external cue (Sasaki, Janetopoulos et al. 2007, Bosgraaf and Van Haastert 2009, Arai, Shibata et al. 2010, Xiong, Huang et al. 2010).

The signal transduction network connects to the cytoskeletal network, and controls organization of the acto-myosin cytoskeleton which drives cell migration. In *Dictyostelium* and mammalian cells, the cytoskeletal network is made up several components which include Rho family G proteins, myosin II, SCAR/WAVE complex, Arp 2/3 complex and coronin (Figure 1B) (Wilkins and Insall 2001, Alvarez-Gonzalez, Meili et al. 2014). Of these components, the Rho family GTPases are a crucial convergence point of migration-associated signaling. In mammals, cell migration-related research has been focused on Rac1, RhoA and Cdc42 proteins of the Rho family whereas 15 Rho family proteins are present in *Dictyostelium*. These proteins act on a number of effectors, thereby regulating protrusion, adhesion and polarization during migration (Lim, Spiegelman et al. 2002). Studies have shown that there is functional conservation between mammalian Rac1 and RhoA and *Dictyostelium* Rac1A/C and RacE, respectively (Filic, Marinovic et al. 2012, Wang, Ku et al. 2013, Wang, Senoo et al. 2013).

In migrating cells, many components of the signal transduction network selectively translocate to, or are activated on, protrusions tips while others, initially present on the cortex dissociate from the protrusions. These sets of components are referred to as “front” or “back”, respectively (Figure 2). For example, “front” biosensors for Ras or PI3K activation and PIP3 accumulation reside in the cytosol and are recruited to the tips of pseudopodia as protrusions form. On the other hand, “back” proteins such as PTEN and myosin are present uniformly in the cortex and dissociate from the regions where protrusions are formed (Parent 2004, Kriebel, Barr et al. 2008). Such complimentary distribution of front and back components is observed in an extensive set of other morphological changes. For example, the pattern is preserved in macropinosomes and pseudopods and during cytokinesis where front molecules accumulate at the poles of the dividing cell and back molecules localize to the cleavage furrow (Figure 2) (Janetopoulos, Borleis et al. 2005). The same complementary pattern of front events and back events is also observed in fused giant *Dictyostelium* cells (see below). Furthermore, in presence of a global chemoattractant stimulation, all front components translocate from the cytosol to distribute uniformly over the cortex or membrane whereas the back molecules fall off from the cell periphery into the cytosol (Figure 2). When latrunculin A-treated cells are subjected to a chemoattractant gradient, membrane patches for the front components are enhanced at the high side of the gradient, and suppressed at the low side. The back components followed an exactly complementary localization pattern on the membrane in response to a spatial gradient (Figure 2) (Parent, Blacklock et al. 1998, Iijima and Devreotes 2002, Iijima, Huang et al. 2004, Janetopoulos, Ma et al. 2004, Sasaki, Chun et al. 2004). A comprehensive list of signaling components that translocate to front or back of cells is provided previously (Swaney, Huang et al. 2010).

Asymmetric accumulation of front and back components is crucial for promoting actin polymerization and producing cellular protrusions for cell migration. In cells expressing constitutively active RasC (Q62L), F-actin polymerization appears at ectopic sites around the cell periphery resulting in increased protrusions and reduced directionality to the chemoattractant source (Cai, Das et al. 2010). Excess accumulation of PIP3 along the entire cell periphery in neutrophils lacking Ship1 or *Dictyostelium* lacking PTEN, gives rise to ectopic lateral pseudopodia outside the leading edge. If these cells are treated with a PI3K inhibitor, this phenotype is reverted to a single anterior pseudopod in the cells (Funamoto, Meili et al. 2002, Iijima and Devreotes 2002, Chen, Janetopoulos et al. 2003, Nishio, Watanabe et al. 2007). Various studies involving uniform activation or pharmacological inhibition of PI3K have shown that altering levels of PIP3 alone is sufficient to affect directed and random migration in neutrophils, fibroblasts, germ cells, cancer cells, and *Dictyostelium* (Chen, Janetopoulos et al. 2003, Dumstrei, Mennecke et al. 2004, Ferguson, Milne et al. 2007, Hoeller and Kay 2007, Inoue and Meyer 2008, Devreotes and Horwitz 2015). In cells lacking the 5-phosphatase, Dd5P4, depletion of PI(3,4)P2 leads to increased Ras activity, cell spreading and aberrant migratory behavior (Li, Edwards et al. 2018). Therefore, role of signal transduction networks in cell migration across various species is well-established.

Role of excitability in *Dictyostelium* and mammalian cells

Although the networks shown in Figure 1B depict a linear interaction between inputs, signal transduction and cytoskeletal events, such a linear interaction is not sufficient to explain increasing instances of actin wave propagation. Vicker and colleagues (Vicker 2002) provided the first evidence of spiral localization patterns of actin filament assembly in vegetative-stage *Dictyostelium* cells. Actin wave generation and propagation in *Dictyostelium* cells was further characterized and confirmed by Gerisch *et al* (Bretschneider, Diez et al. 2004, Gerisch 2010). Coordinated waves of Ras activity, PIP3, PTEN and actin were observed in *Dictyostelium* which provided a basis for modeling the nonlinear interactions that produce spatio-temporal patterns in the actin system of cells (Arai, Shibata et al. 2010, Xiong, Huang et al. 2010, Gerisch, Schroth-Diez et al. 2012, Xiong, Xiao et al. 2016). Signal transduction or cytoskeletal waves were then reported by a growing number of studies in various types of mammalian cells such as neutrophils (Weiner, Marganski et al. 2007, Hepper, Schymeinsky et al. 2012), macrophages (Masters, Sheetz et al. 2016), fibroblasts (Case and Waterman 2011), Xenopus eggs (Bement, Leda et al. 2015), mast cells (Wu, Wu et al. 2013, Xiong, Xiao et al. 2016, Colin-York, Li et al. 2019), keratocytes (Barnhart, Lee et al. 2011), cultured neurons (Winans, Collins et al. 2016), and cancer cells (Marchesin, Montagnac et al. 2015). Waves of signaling (PIP3) and cytoskeletal components (actin filaments) show a distinct dynamic pattern with respect to each other (Gerisch, Ecke et al. 2011, Gerhardt, Ecke et al. 2014). In fused *Dictyostelium* cells, F-actin (LimE) appears as narrow “leading” and “trailing” bands separated with intermediate intensity while PIP3 (PHcrac) initiates with the leading edge and trails off through the entire region. PIP3/F-actin waves in fused *Dictyostelium* show similar patterns in mammalian cells such as macrophages. An example is shown in Figure 3.

To explain wave propagation, and other features of the signal transduction networks (shown in Figure 1B) including spontaneous activations, and refractory periods, we have proposed that this network is excitable. Within the signal transduction excitable network (STEN), an activator triggers a fast, autocatalytic loop that generates positive feedback, and a slower inhibitor forms a negative feedback loop. As the activator and inhibitor diffuse, the activities of these processes travel throughout the medium in the form of propagating wave. A number of mathematical models consisting of such reaction–diffusion equations for actin waves have also been proposed to capture wave formation and propagation (Meinhardt and de Boer 2001, Hecht, Kessler et al. 2010, Xiong, Huang et al. 2010, Bement, Leda et al. 2015, Miao, Bhattacharya et al. 2019). 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 states, respectively. The B and F states create 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 regions. The trailing R region ensures unidirectionality of the waves and their annihilation upon crossing each other (Miao, Bhattacharya et al. 2017).

Studies in multiple labs are beginning to delineate the architecture of the signal transduction and cytoskeletal networks. In STEN, evidence suggests that a mutually exclusive interaction

between Ras/Rap and PI(4,5)P2/PI(3,4)P2 can be assigned to F and B, respectively, whereas there is negative feedback through PKBA/PKBR1, which is assigned to R. Interestingly, PIP3 as an activator of PKBA, plays a negative role in STEN, while it is also an important positive regulator to actin polymerization (Figures 1B and 4). The cytoskeletal network is also excitable and is referred to as the cytoskeletal excitable network (CEN) (Figures 1B and 4) (Li, Edwards et al. 2018, Miao, Bhattacharya et al. 2019). The activities of CEN are more localized and rapid than those of STEN. Studies in *Dictyostelium* have shown that in the absence of signal transduction, these cytoskeletal events generate short, narrow protrusions, whereas coupling of STEN and CEN produces waves at the edge of cells followed by forward expansion of the membrane in the form of pseudopodia or broad lamellipodia-like protrusions (Vicker 2002, Huang, Tang et al. 2013, Shi, Huang et al. 2013, Tang, Wang et al. 2014, Miao, Bhattacharya et al. 2019). Such correlations between signal transduction and actin waves, and leading edge protrusions are also found in mammalian cells such as neutrophils (Weiner, Marganski et al. 2007), fibroblasts (Zhang, Lyu et al. 2018, Jalal, Shi et al. 2019), keratocytes (Barnhart, Lee et al. 2011) and cancer cells (Yang, Bhattacharya et al. 2018).

The non-linear feedback models suggest that alteration in individual components can have a significant impact on the overall excitability of the networks. Experimental evidence for this was provided in a recent study where the threshold for STEN activation was synthetically reduced, by either decreasing PIP2 level or increasing Ras/Rap activities at the cell cortex, which resulted in significantly increased speed and range of F-actin waves in *Dictyostelium* cells. Such a change in wave propagation resulted in expansion of small, cup-like protrusions to very wide, lamellipodia-like protrusions, and ultimately, caused changes in cellular migratory modes from amoeboid to keratocyte-like and oscillatory (Figure 5) (Miao, Bhattacharya et al. 2017, Miao, Bhattacharya et al. 2019). This work further supports the idea that STEN-CEN coupling generates sustained protrusions of migrating cells. Moreover, such abrupt and reversible changes in migratory modes between amoeboid and gliding indicate that migratory behaviors demonstrated by various eukaryotic cells could arise from a basic mechanism of STEN-CEN coupling.

Dictyostelium makes predictions about eukaryotic migration

We propose that, as in *Dictyostelium*, wave patterns of signal transduction components control protrusive activities in mammalian cells. It has been previously reported that local production of PIP3 or Rac1 activation, by optogenetics, is sufficient to initiate actin growth cone-like “waves” in developing neurons or reorient polarity and guide migration in neutrophils (Kakumoto and Nakata 2013, Graziano, Gong et al. 2017). Moreover, the ability of manipulations of key signaling molecules or enzymes to create migratory and hyperactive phenotypes in mammalian cells, can be interpreted as changes of wave propagation. Examples include SHIP1 or PTEN deletions in neutrophils show increased motility and recruitment to inflamed sites (Sarraj, Massberg et al. 2009, Lam, Yoo et al. 2012), overexpression of cancer-associated, membrane translocation-incompetent PTEN mutations showed increased cell proliferation and migration in breast epithelial cells (Nguyen, Yang et al. 2015), and mutations of K-Ras promote migration and invasion in various cancers (Mann, Ying et al. 2016, Chu, Lin et al. 2018, Kang, Zhang et al. 2018, Millien, Cao et al. 2018,

Stuelten, Parent et al. 2018). These studies point towards the possibility that STEN is the integration site of extrinsic cues which control migration. There is an increasing appreciation of the ability of cells to integrate environmental signals, such as chemoattractant stimuli, electric fields and mechanical forces, and to move accordingly. Integration of these environmental signals with STEN and CEN, and the various regulatory feedback loops involved between them may be sufficient to explain the vast array of protrusions and migratory modes observed in diverse eukaryotic cells under physiological and pathological conditions.

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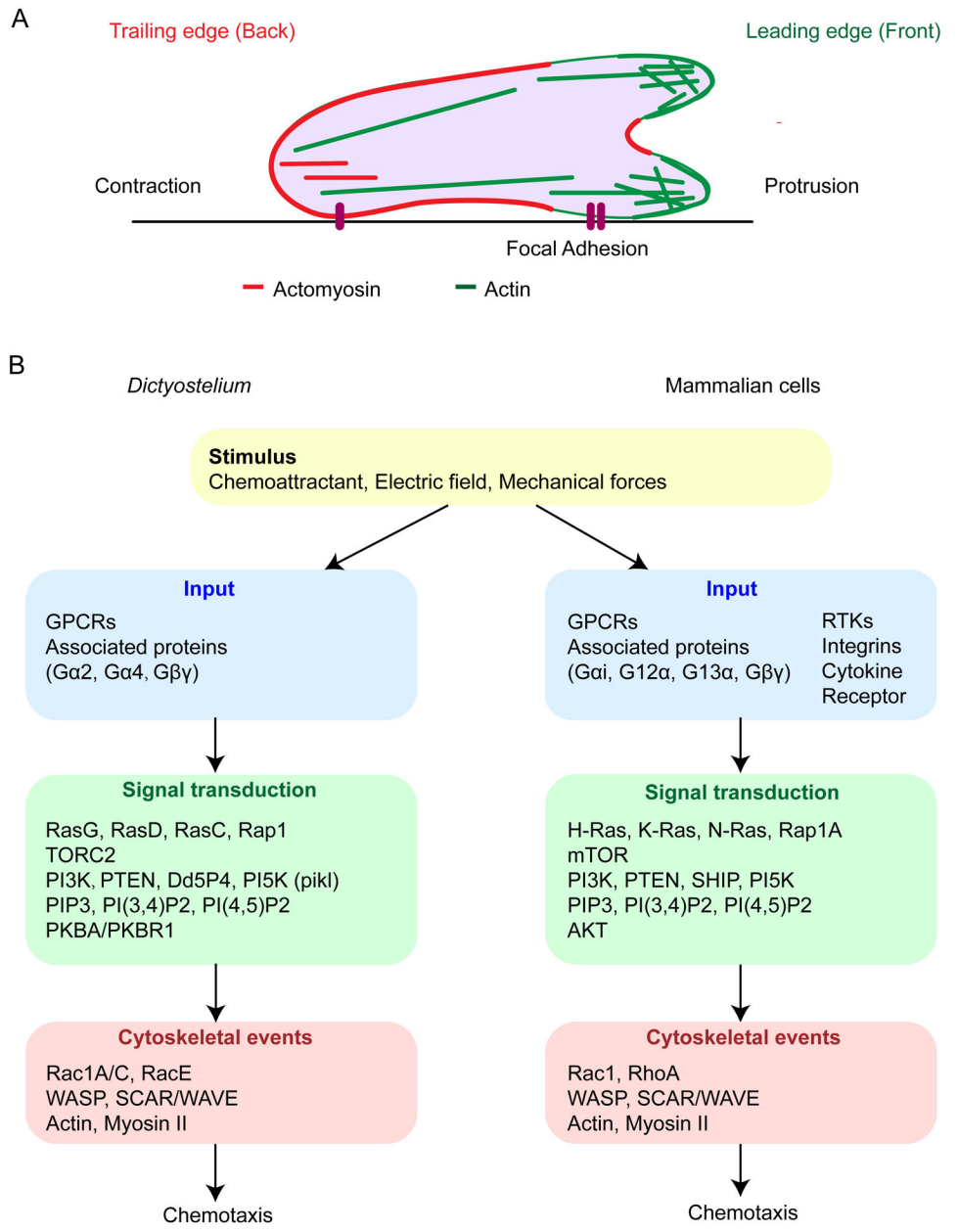

Figure 1. Molecular components involved in eukaryotic migration.

(A) Eukaryotic migration is achieved by extending actin-rich protrusions at the leading edge of the cell (as shown in green), coordinated with actomyosin-based contraction at the trailing edge (denoted in red). These cells develop active sites for actin polymerization, called focal adhesions, underneath the leading edge for integrin-dependent adhesion and migration. (B) Independent genetic and biochemical experimentation have identified various components involved in directed cell migration which can be grouped into 3 networks- input, signal transduction, and cytoskeletal events. Some of the important components for each of these networks have been highlighted in the cartoon. A variety of external stimuli, such as chemoattractant (chemicals), electric fields and mechanical forces, locally activate the signal transduction networks through input networks, leading to cytoskeletal events such as F-actin

polymerization at the front and actomyosin-based contraction at the back of the cell. This coordinated activation of these networks results in chemotaxis (directed cell migration) and is functionally conserved in *Dictyostelium* (left) and mammalian cells (right).

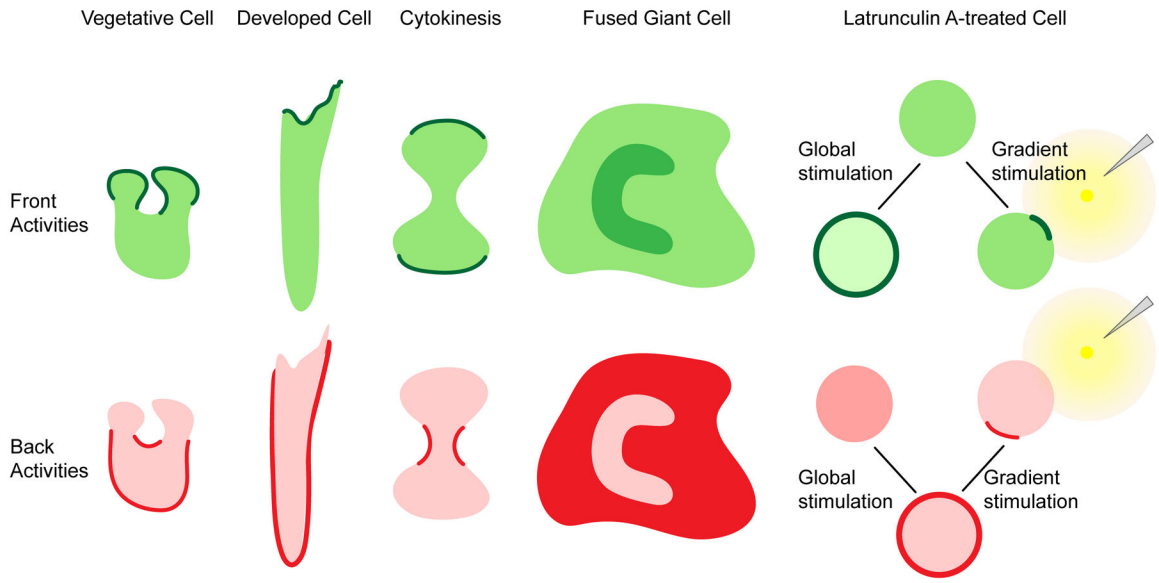

Figure 2. Complementary distributive pattern of front and back activities in *Dictyostelium* cells undergoing various morphological changes.

Front activities, such as Ras or PI3K activation, occur at the protrusions of migrating vegetative or developed cells, respectively (denoted in dark green, top row). These front activities are complemented with back activities, such as dissociation of PTEN, at the cellular protrusions (denoted in red, bottom row). During cytokinesis, these front molecules are found at the poles of the dividing cells and the back molecules accumulate at the cleavage furrow. This complimentary pattern of front and back molecules is conserved in fused *Dictyostelium* cells. Upon global or gradient chemoattractant stimulation, latrunculin A-treated cells also show opposite distribution of front and back activities.

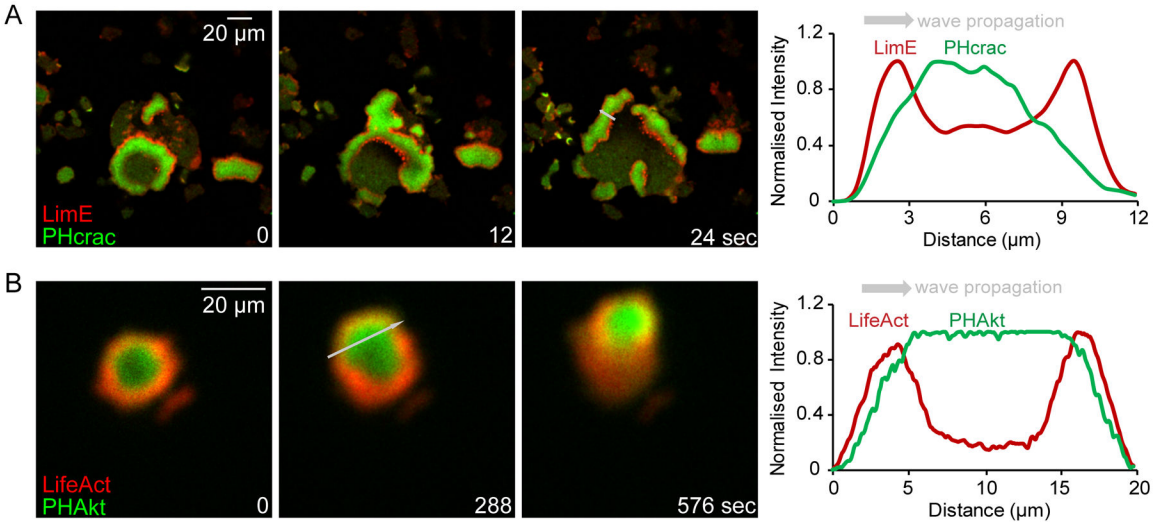

Figure 3. Conservation of PIP3 and F-actin waves in *Dictyostelium* and mammalian cells.

(A) Time lapse merged confocal images showing distribution of LimE (red) and PHcrac (green) in waves at the basal surface of a migrating fused *Dictyostelium* cell (left). Intensity plot across the white arrow in image “24 sec” (right). (B) Time lapse merged confocal images of LifeAct (red) and PHAkt (green) in waves at the basal surface of a RAW 264.7 macrophage cell (left). Intensity plot across the white arrow in image “288 sec” (right).

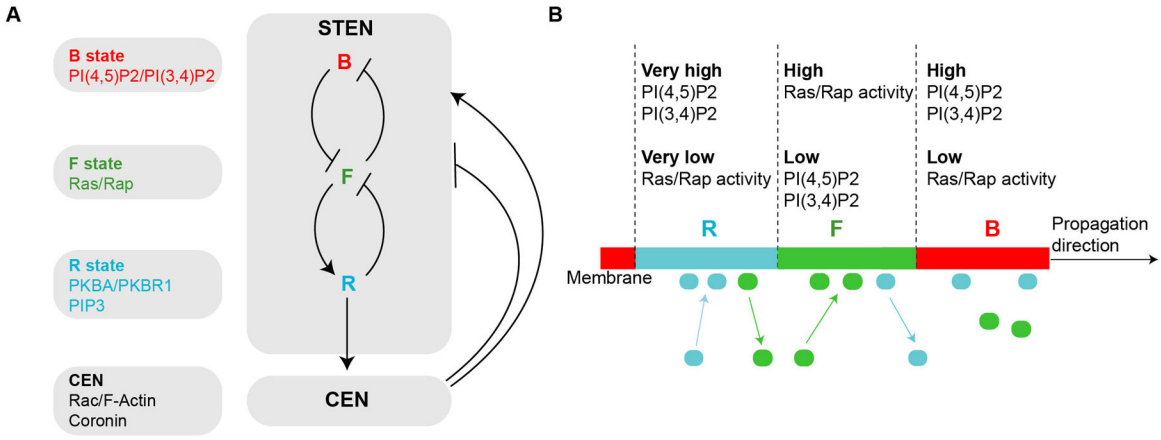

Figure 4. Cartoon depicting molecular architecture of STEN and the various feedback loops involved.

The positive feedback in STEN is brought about by mutual inhibition of active (F; activation of Ras/Rap) and inactive (B; PIP2) states at the cell cortex, and a delayed negative feedback from R (refractory), due to delayed PKB activation by PIP3, to F state. The PKBs feeds into CEN and promotes F-actin polymerization which, in turn, provides a fast positive and slow negative feedbacks to STEN. Abbreviations: STEN, signal transduction excitable networks; CEN, cytoskeletal excitable networks.

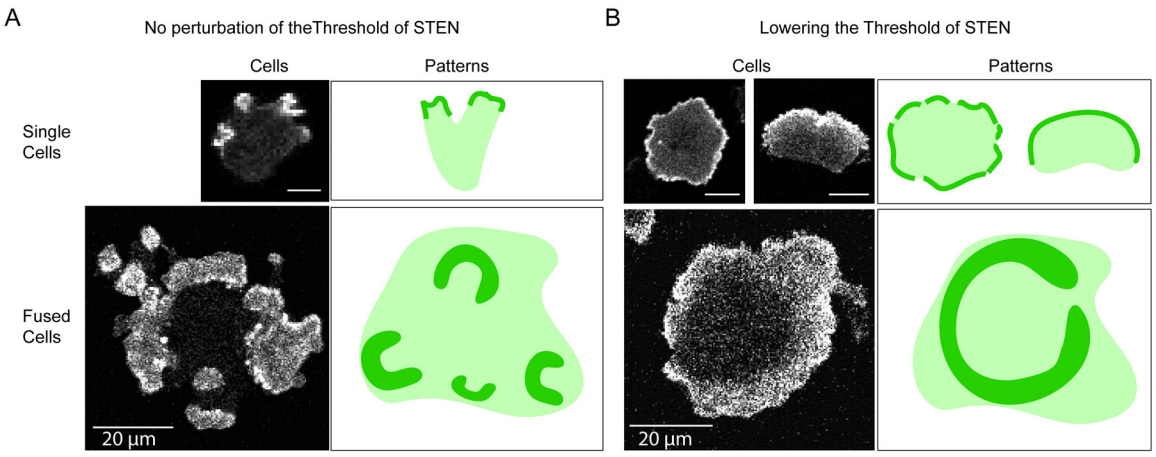

Figure 5. Perturbation of STEN threshold alters wave behavior and ultimately changes protrusion pattern necessary for cell migration.

(A) Left; confocal images showing LimE patterns in the protrusions of single (top) or basal surface of fused (bottom) *Dictyostelium* cells, in absence of any synthetic perturbation to the threshold for STEN activation. Right; cartoon depicting the cortical wave patterns corresponding to cellular morphology in the 'unperturbed' single (top) or fused (bottom) cells. (B) Left; confocal images showing LimE distribution on the basal surface of single (top) or fused (bottom) *Dictyostelium* cells, upon lowering of the threshold for STEN activation. In single cells, it causes the size of cellular protrusions to expand from small macropinosomes or pseudopodia (as seen in unperturbed cells) to wide, sheet-like protrusions resembling lamellipodia. This ultimately changes the migratory mode of the cells from amoeboid to oscillatory or fan-shaped. Right; cartoon depicting the cortical wave patterns corresponding to cellular morphology in the single (top) or fused (bottom) cells.