Navigating signaling networks: chemotaxis in *Dictyostelium discoideum*

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Studies of chemotaxis in the social amoeba *Dictyostelium discoideum* have revealed numerous conserved signaling networks that are activated by chemoattractants. In the presence of a uniformly distributed stimulus, these pathways are transiently activated, but in a gradient they are activated persistently and can be localized to either the front or the back of the cell. Recent studies have begun to elucidate how chemoattractant signaling regulates the three main components of chemotaxis: directional sensing, pseudopod extension, and polarization.

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Introduction

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Chemotaxis is the directed migration of cells in gradients of signaling molecules, an essential biological process that underlies morphogenesis during development, and the recruitment of immune cells to sites of infection. It is also an important component of pathological conditions, including metastasis and chronic inflammatory diseases. Though the humble amoeba *Dictyostelium discoideum* is more at home in the soil than in the lab, it has for many years proved itself as a remarkable model organism for studying this process [1]. These cells survive by feeding on yeasts and bacteria that they track down by chemotaxing towards secreted metabolites. This organism, however, is best known for its response to starvation, which turns these solitary cells into socialites. Up to a million cells aggregate and form multicellular structures containing spores that are resistant to harsh environmental conditions. Chemotaxis, in this case to cAMP, is also at the heart of this stage of the lifecycle. The ability to combine genetic, biochemical and cell biological analyses in this system has facilitated the discovery of many key signaling pathways that are conserved in higher eukaryotes and has provided a framework to model chemotaxis. This review summarizes our current understanding of this process, with a particular focus on *D. discoideum*.

Chemotactic signaling networks

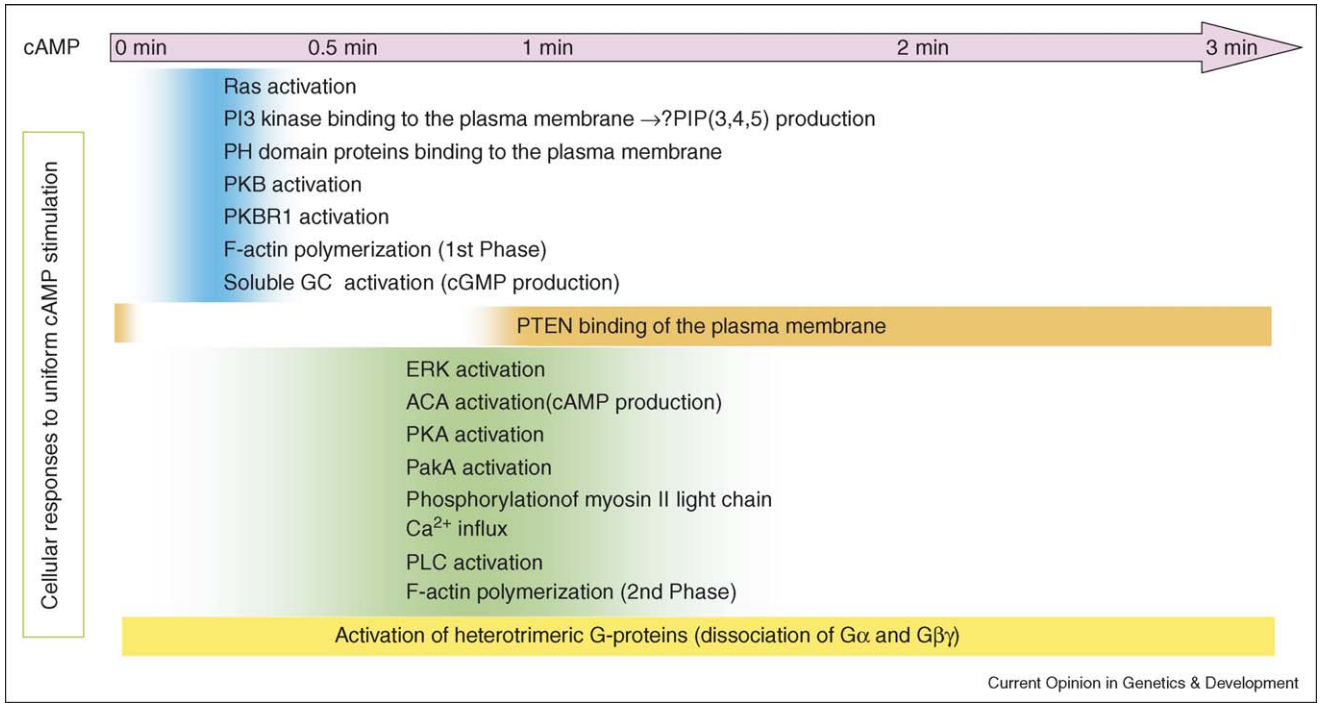
Studies with *D. discoideum* have enabled us to uncover some of the fundamental signaling pathways that mediate chemotaxis (Figure 1) [1]. G-protein-coupled receptors at the cell surface interact with chemoattractants, and this leads to guanine nucleotide exchange in the α-subunit of the heterotrimeric G-proteins and dissociation of the βγ dimer. This activates multiple signaling pathways, such as those that lead to the production of second messenger molecules (e.g. phosphatidylinositol-3,4,5-triphosphate [PIP3], cAMP and cGMP) and the activation of small G-proteins. Furthermore, ion channel permeability is regulated to generate a Ca^{2+} influx and H^{+} efflux upon stimulation. These responses are triggered by changes in receptor occupancy and subside or adapt upon uniform stimulation. The heterotrimeric G-protein subunits remain dissociated in the presence of ligands, indicating that adaptation occurs downstream. Recent work has begun to elucidate how these signaling networks contribute to the processes involved in chemotaxis.

The directed movement of cells during chemotaxis can conceptually be viewed as the integration of three separate processes. First, there is *directional sensing*, the capacity of cells to determine the direction of the concentration gradient. This can be thought of as the cell's compass. Second, cells elaborate periodic *pseudopod extensions* or membrane projections. These are the basic unit of motility, and in amoebae are produced at approximately one minute intervals. Third, there is *polarization*, or stable changes in morphology, and the localization of proteins to the front and back of cells. Polarization enhances migration by generating persistent movement in a specified direction. Periodic pseudopodia formation and polarization can occur in a uniform concentration of chemoattractant, whereas directional sensing requires an external gradient. Working together, these three modules combine to make chemotaxis a highly sensitive and robust process.

Directional sensing

The best-studied indicator of directional sensing is the phospholipid PIP3, which specifically accumulates at the front of a variety of cells when exposed to appropriate gradients. In *D. discoideum*, this is achieved by the coordinated regulation of the enzymes phosphatidylinositol

Figure 1



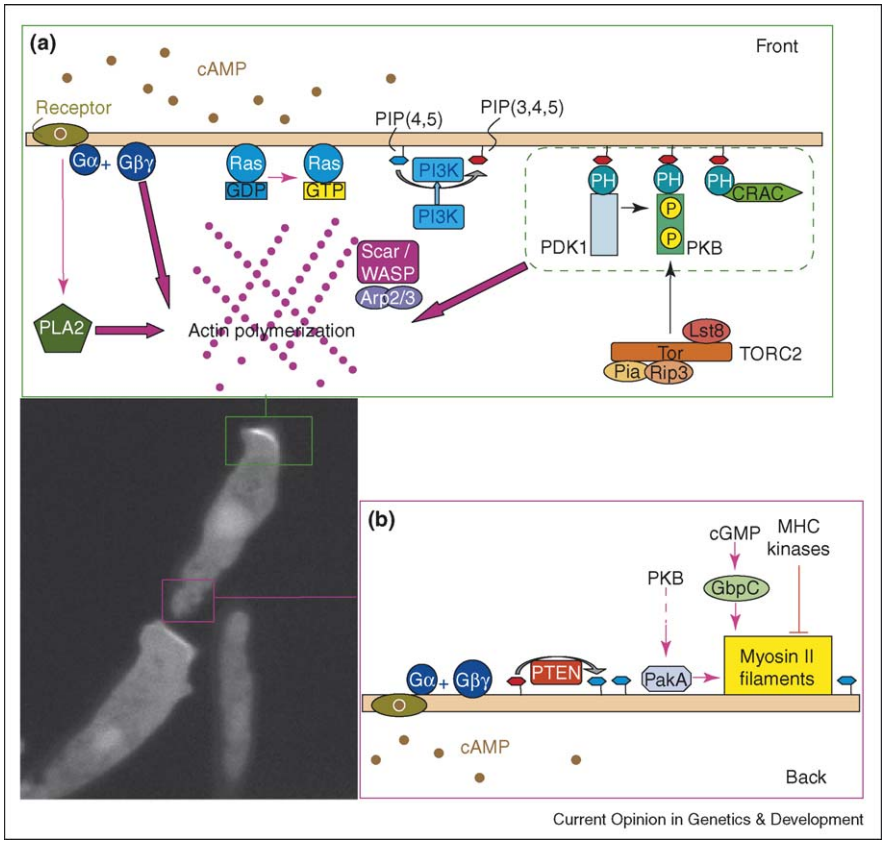
Uniform chemoattractant-stimulation triggers the activation of multiple signaling networks. Following the timescale represented by the pink arrow, most responses are transient and can be classed as early (10–30 seconds, blue shading) or late (30–90 seconds, green shading). Note that chemoattractants induce two phases of actin polymerization: a rapid early peak followed by a later second peak. PTEN transiently dissociates from the plasma membrane upon stimulation (orange bar), whereas the heterotrimeric G-proteins remain constantly activated as long as chemoattractant is present (yellow bar).

3-kinase (PI3K), which produces PIP3 by phosphorylating PIP2, and PTEN (phosphatase and tensin homologue deleted on chromosome ten), which catalyzes the reverse reaction [2–4]. At the leading edge, where chemoattractant concentrations are highest, Ras is activated and PI3K is recruited from the cytoplasm (Figure 2) [5•]. Conversely, PTEN falls off the plasma membrane at the front but remains strongly bound at the back. As a result, PIP3 accumulation is restricted to the leading edge and can be compared to the 'needle' of the cell's compass. These events also occur in cells treated with inhibitors of actin polymerization, indicating that neither movement nor actin polymerization are required for directional sensing. The best evidence for the importance of this pathway comes from cells lacking PTEN. In these cells, broadly distributed PIP3 promotes actin polymerization and pseudopod extension all around the perimeter, and chemotaxis is severely impaired [4].

Although the importance of the PIP3 compass is appreciated for most chemotactic cells, cells differ in their ability to amplify the asymmetry of the gradient by concentrating PIP3 at the front. For example, in phagocytic cells, such as neutrophils and *D. discoideum*, the distribution of PIP3 is 3–6 times steeper than the external gradient, whereas the PIP3 distribution in fibroblasts mirrors that of the gradient [6,7•,8]. Interestingly, the enhanced ability to amplify the gradient correlates with superior chemotactic potential. Phagocytic cells can perceive 1–2% differences in receptor occupancy in gradients with midpoint concentrations that can range over four orders of magnitude. By contrast, fibroblasts require much steeper gradients and can only sense direction in a narrow concentration range [7•]. A fundamental difference that could explain these observations is that, in contrast to PIP3 production in *D. discoideum* and neutrophils, PIP3 production in fibroblasts does not adapt. In the absence of adaptation, it is more difficult for cells to distinguish direction in gradients with high midpoint concentrations, because signaling approaches a maximum level throughout the cell. This finding is also consistent with one of the proposed models of directional sensing — the local excitation–global inhibition model — and suggests that fibroblasts lack the mechanism for 'global inhibition'. Readers are directed to the following review for further discussion [9•].

The regulation of PI3K and PTEN localization is a key component of this directional sensing system. The amino terminus of *D. discoideum* PI3K is necessary and sufficient for membrane binding, and in contrast to mammalian PI3K, no regulatory subunits have been identified [2].

Figure 2



In a gradient, chemotactic cells persistently activate specific pathways at the front and back. At the front **(a)**, Ras is activated and PI3K is recruited to the plasma membrane, leading to the accumulation of PIP3. PIP3 interacts with PH domain-containing proteins such as PDK1, PKB and CRAC. PKB is phosphorylated and activated by PDK1 and the TORC2 complex and is an important regulator of actin polymerization. A PIP3-independent signaling pathway involving a calcium-independent PLA2 enzyme also regulates actin polymerization and membrane extension at the front. Additional pathways might exist, because cells lacking both PI3K and PLA2 are able to move and polymerize actin. Scar–WASP proteins acting through the Arp2–Arp3 complex are also thought to be important regulators of actin polymerization. At the back **(b)**, PTEN remains membrane-bound and degrades PIP3, whereas myosin II is assembled into contractile filaments that suppress pseudopod formation and promote retraction of the cell's rear. PakA, the activity of which is promoted by PKB, and the cGMP binding protein GbpC promote the assembly and activity of myosin II, which is antagonized by myosin heavy chain kinases present at the front. Abbreviations: CRAC, cytosolic regulator of adenylyl cyclase; PakA, p21 activated kinase A; Pia, pianissimo; PI3K, PI3 kinase; PKB, protein kinase B; PLA2, phospholipase A2; PTEN, phosphatase and tensin homolog on chromosome 10; Rip3, Ras-interacting protein 3; TORC2, Tor2 complex.

Membrane binding of PTEN requires the presence of an amino-terminal PIP2 binding domain and appears to be regulated by phosphorylation [10,11]. Using total internal reflection microscopy, it was shown that individual PTEN molecules bind to the plasma membrane for only several hundred milliseconds, indicating that membrane binding is a highly dynamic process. This might facilitate the rapid changes in PTEN distribution observed when gradients change direction [6]. Identifying the binding sites for PTEN and PI3K and how they are regulated is a key objective for future research.

Emerging data, however, indicates that there is more to the story of chemotaxis than PIP3. In phagocytic cells, inhibiting PIP3 production has only marginal effects on chemotaxis. Cells move slower and take slightly longer to change direction when the chemoattractant source is moved, raising the possibility that alternative directional sensing pathways exist [12]. New data from our lab indicate that the calcium-independent phospholipase A_2 enzyme might be part of such a pathway. Cells lacking the gene encoding this enzyme perform chemotaxis efficiently in normal conditions but are severely impaired when PI3K activity is inhibited (L Chen, unpublished). Directional sensing could also involve the homolog of the Shwachman–Bodian–Diamond syndrome protein, which causes directional-sensing defects when mutated in human neutrophils [13].

Pseudopod extensions

Cell movements and shape changes are driven largely by remodeling of the actin cytoskeleton. At the leading edge,

actin polymerization mediated by the Arp2–Arp3 complex produces a network of branched filaments that lead to pseudopod extension. Recent studies have examined several regulators of the Arp2–Arp3 complex, in particular the WASP (Wiskott–Aldrich syndrome protein) and Scar (suppressor of cAMP receptor) family of proteins. The *D. discoideum* homologs of WASP localize to both poles of migrating cells, and cells with lowered levels of WASP are unable to aggregate [14]. This correlates with a lower basal level of F-actin and a subtle defect in cAMP-induced actin polymerization. Scar was initially identified in *D. discoideum* as a suppressor of cells lacking the cAMP receptor cAR2 (cAMP receptor 2). As in mammalian cells, *D. discoideum* Scar is part of a multiprotein complex consisting of NapA (Nck-associated protein A), Pir121 (p53-inducible mRNA 121), Abi1–Abi2 (ABL-inducible mRNA 1–2) and HSPC300 (haematopoietic stem cell progenitor 300). Knockouts of Scar and NapA move more slowly but are able to chemotax and aggregate [15]. A stronger phenotype is seen in the absence of Pir121, resulting in Scar over-activation and the widening and splitting of pseudopods [16].

Exactly how PIP3 promotes actin polymerization at the leading edge remains unclear, but it is likely that PIP3 exerts its effects by recruiting pleckstrin homology (PH) domain-containing proteins to the plasma membrane (Figure 2). Recent studies have suggested several different mechanisms. First, PH domain-containing proteins might regulate Scar–WASP activity by acting as Rac guanine nucleotide exchange factors (GEFs), thus restricting activation to the leading edge. In neutrophils, a strong candidate is P-Rex, a RacGEF activated by Gβγ subunits and PIP3. A direct homolog of this protein has not been identified in *D. discoideum*, but a recently identified protein, RacGEF1, is reported to localize at the front of cells and activate RacB [17]. Second, we hypothesize from recent data that protein kinase B (PKB; also known as Akt) plays a role downstream of PIP3. This protein is recruited to the front of *D. discoideum* cells and the knockout mutant has a chemotaxis phenotype [18] (L Chen and PN Devreotes, unpublished). Furthermore, recent studies have linked the regulation of PKB with two *D. discoideum* genes, *pianissimo* and *rip3*, which were previously shown to have roles in chemotaxis and actin polymerization [19•]. These two proteins are part of a multiprotein complex with the Tor kinase (target of rapamycin), which was initially identified in yeast and is now thought to activate PKB by phosphorylating the residue corresponding to serine 473 of human PKB. Finally, other PH domain proteins, such as CRAC (cytosolic regulator of adenylyl cyclase) and PhdA, localize to the leading edge and are required for efficient chemotaxis [20].

Regulation of the cytoskeleton at the back and sides are equally as important as the events occurring at the front. Here, the focus is on preventing lateral extensions that point away from the direction of the gradient and supplying contractile force to retract the rear of the cell. *D. discoideum* cells lacking the *myosin II heavy chain* (*MHC*) gene extend numerous lateral and even some vertical pseudopods [21]. Consequently, whereas wild type cells move persistently towards chemoattractant sources, *mhc*–frequently change direction and migrate at about half the normal velocity. A similar phenotype is seen in cells lacking PakA, guanylyl cyclase activity or the cGMP binding protein GbpC (Figure 2b). The defects in these mutants correlate with the impaired recruitment of myosin II to the cortical cytoskeleton [22,23]. Recruitment is also inhibited by MHC phosphorylation. Thus, the localization of an MHC kinase to the front of the cell might act as a mechanism to confine myosin to the back and side of cell [24]. By contrast, phosphorylation of myosin regulatory light chain (MLC) promotes myosin II activity. Again, cGMP is a key regulator of this kinase, because mutants with decreased cGMP phosphodiesterase activity have increased MLC phosphorylation [22]. The function of myosin II is conserved in neutrophils although, in this case, RhoA-mediated phosphorylation of MLC appears to be the dominant regulatory event [25]. Other genes have been reported to suppress lateral pseudopods (e.g. adenylyl cyclase, a Na^+–H^+ exchanger, and sphingosine-1-phosphate lyase), although the mechanisms of suppression in these cases remain unclear [26–28].

Polarization

The elongated cell morphologies of neutrophils and starved *D. discoideum* referred to as polarization contribute to chemotaxis by facilitating faster migration and greater persistence in direction. Acquiring polarity is thought to involve suppression of lateral pseudopods (see above), as well as positive feedback loops that occur at the front and back and which amplify the cell's asymmetry. This is suggested by the observations of how polarization affects the response of cells to changes in the direction of the chemoattractant gradient [12]. The more polarized the cell, the longer it takes to respond to changes. Highly polarized cells, such as 7-hour-starved amoebae, maintain the same leading edge and turn towards the new direction, suggesting that the anterior region is more sensitive to chemoattractants. By contrast, less-polarized cells, such as 5-hour-starved *D. discoideum*, respond by retracting existing pseudopods and extending new projections in the correct direction. This is driven by redistribution of PI3K, PTEN and PH-domain proteins, and it achieves a more rapid reorientation of the cell than by turning. These components, however, are relocalized much more rapidly when polarity is abolished by treating cells with pharmacological inhibitors of actin polymerization (e.g. latrunculin A) [6]. This suggests that actin cytoskeleton-dependent feedback loops at the front and back of the cell stabilize intracellular asymmetries. An example of such a feedback system was recently discovered in *D. discoideum*, in which the binding of PI3K to the membrane is

enhanced by actin polymerization, which leads to increased PI3K binding and further actin polymerization [5•]. Similar mechanisms are thought to occur in neutrophils [25].

Recent studies have also shown that PIP3 is an important marker of polarity in other systems, indicating that the mechanisms of directional sensing and polarization used during chemotaxis have more general functions. For example, during cytokinesis, PIP3 accumulates at the poles and is required for efficient cell division whereas, in phagocytosis, PIP3 accumulates at the edges of the phagocytic cup [29•,30•]. As in chemotaxis, the local PIP3 levels are thought to be controlled by the reciprocal regulation of PI3K and PTEN localization.

Conclusions

In summary, chemotaxis can be viewed as a modular process composed of directional sensing, pseudopod extension, and polarization. Each of the modules arises from a complex network of signaling pathways that are temporally and spatially regulated. In many ways, we are only starting to understand how this signaling network produces directed migration but, as in the past, we are hoping that the amoeba *Dictyostelium discoideum* will show us the way forward.

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- •• of outstanding interest

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