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Bidirectional molecular transport shapes cell polarization in a two-dimensional model of eukaryotic chemotaxis

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HIGHLIGHTS

- We describe cell polarization as an intracellular and intramembrane signal feedback system.
- The Lattice–Boltzmann numerical method is applied for solving coupled reaction–diffusion equations.
- The results are in good agreement with well-known experimental ones.
- The model exhibits novel dynamics of switch-like polarization patterns.

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ABSTRACT

Chemotacting eukaryotic cells can sense shallow gradients of chemoattractants and respond by assuming an asymmetric shape with well-defined front and back regions. Such a striking polarization phenomenon is produced largely through the interconversions and interactions between several cellular components, including Rac GTPase (Rac), phosphoinositide 3-kinase (PI3K), tensin homology protein (PTEN), phosphatidylinositol 3,4,5-trisphosphate ($PI(3,4,5)P_3$) and phosphatidylinositol (4,5)-bisphosphate ($PI(4,5)P_2$). Here, we developed a mathematical model of cell polarization by exploring bidirectional molecular transport that arose from phosphoinositides (PIs) and Rac-mediated feedback loops. We assumed a static gradient of activated Rac derived from an external signal field as the internal trigger signal. The evolution of $PI(3,4,5)P_3$ and $PI(4,5)P_2$ along with PI3K and PTEN that act as activator and inhibitor, respectively, were described by a pair of coupled transient reaction-diffusion equations. The entire system was solved using a Lattice–Boltzmann method with an embedded Monte-Carlo method to track the stochastic translocation behaviors of discrete PI3K/PTEN molecules. We first showed that, upon a graded external stimulus, the Rac to $PI(3,4,5)P_3$ cascade exhibited a short range positive-feedback loop, while the PTEN to $PI(4,5)P_2$ cascade contributed another long range negative-feedback loop, which dominated the "forward" and "backward" molecular transport, respectively. Second, polarization was governed by the ratio of [PI3K] to [PTEN], and manifested a switch-like behavior. Third, with a uniform stimulus, spontaneous polarization could occur in PTEN-deficient cells.

1. Introduction

Chemotaxis, or directed cell movement along a spatial gradient of chemoattractant (Dormann et al., 2002; Fisher et al., 1989; Servant et al., 2000; Song et al., 2006), plays critical roles in many biological processes, including immune responses, cancer metastasis, wound healing, and neuron patterning (Gillitzer and Goebeler, 2001; Isbister et al., 2003; Olson and Ley, 2002; Yamaguchi et al., 2005). For a cell to move directionally as opposed to randomly searching its environment, its locomotion machinery must be accurately oriented. This is accomplished through the initial step of chemotaxis known as polarization, during which chemoattractant spatiotemporally regulates the activity and/or localization of intracellular molecules to induce bidirectional cytoskeleton rearrangements. This results in the formation of a pseudopod ("false foot") at the cell front that faces the chemoattractant gradient and a posterior at the opposite side (Devreotes and Janetopoulos, 2003; Rappel and Loomis, 2009; Ridley et al., 2003; Weiner, 2002). Using pseudopod extension together with posterior retraction, maturation, and breakage of cell–substrate adhesions, a cell starts to move toward the chemoattractant source (Bailly and Condeelis, 2002; Mogilner, 2009; Ridley et al., 2003).

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During the last two decades, investigators have determined the signal transduction cascades that underlie cell polarization, largely by experiments using *Dictyostelium* ameboid cells (Charest and Firtel, 2006; Janetopoulos and Firtel, 2008; Parent and Devreotes, 1999; Willard and Devreotes, 2006). Based on the current information, a simplified version of a polarization cascade can be divided into four stages, which are (I) signal reception, (II) initial signal processing, (III) Rac GTPase regulation, and (IV) cytoskeleton rearrangement (see Fig. 1).

(I) Signal reception: cAMPs, as chemoattractants, are recognized by transmembrane receptors, primarily G protein-coupled receptors (GPCRs) that are uniformly distributed around the cell perimeter (Jin et al., 2000; Servant et al., 1999; Ueda et al., 2001).

(II) Initial signal processing: the activation of GPCRs elicits a persistent dissociation of heterotrimeric G proteins into βγ− and α− subunits that, respectively by driving excitatory and inhibitory pathways, results in an initial biased distribution of phosphatidylinositol 3,4,5-trisphosphate ($PI(3,4,5)P_3$) along the external gradient (Parent and Devreotes, 1999).

(III) Rac GTPase regulation: $PI(3,4,5)P_3$ acts upon guanine nucleotide exchange factors (GEFs) to regulate Rac, a small GTPase of the Rho family (Bos et al., 2007; Pertz, 2010; Raftopoulou and Hall, 2004).

(IV) Cytoskeleton rearrangement: activated Rac interacts with various actin-binding proteins (ABPs), such as SCAR/WASP and Arp2/3 complex, which results in localized F-actin polymerization (Bagorda and Parent, 2008; Charest and Firtel, 2006; Ridley et al., 2003; Sasaki and Firtel, 2006; Stossel et al., 2006); during this process, phosphoinositide 3-kinase (PI3K) are recruited from the cytosol to the cell membrane (Charest and Firtel, 2006) and, after being activated by Rac, catalyze the phosphorylation of phosphatidylinositol (4,5)-bisphosphate ($PI(4,5)P_2$) to produce $PI(3,4,5)P_3$ (Cain and Ridley, 2009; Van Haastert and Devreotes, 2004); the resulting $PI(3,4,5)P_3$ molecules then act as binding sites for various ABPs that, in turn, promote F-actin polymerization, which leads to further membrane recruitment of PI3K (Charest and Firtel, 2006); in addition, PTEN are recruited by $PI(4,5)P_2$ to the cell membrane and dephosphorylate $PI(3,4,5)P_3$ to produce $PI(4,5)P_2$ (Iijima et al., 2002; Leslie et al., 2005; Sulis and Parsons, 2003).

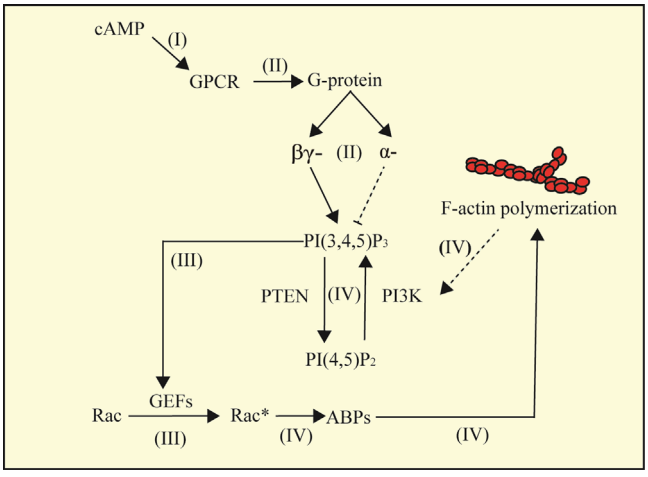

Fig. 1. Simplified schematic diagram of a signal transduction cascade underlying the polarization phase of eukaryotic chemotaxis. The cascade is depicted in four stages: (I) signal reception, (II) initial signal processing, (III) Rac GTPase regulation, and (IV) cytoskeleton rearrangement.

Several different polarization models have been proposed. For example, an early group of Turing-type instability models (Meinhardt, 1999) based on strong autocatalytic positive-feedback loops could exhibit a powerful amplification response for an externally-derived signal. However, these Turing-type models produce spontaneous symmetry breaking on the cellular scale with multiple excited regions. Thus, activation is not limited only to the front or rear region of a cell. A diffusion–translocation model proposed by Postma and van Haastert (2001) simulated localized accumulation of $PI(3,4,5)P_3$ at the front of a cell. This model considered a cytosolic effector molecule (i.e., PI3K) that enhanced receptor-mediated production of $PI(3,4,5)P_3$; thus, recruiting more effector molecules from the cytosol to the membrane. However, it did not address how associated proteins, such as PTEN and $PI(4,5)P_2$, would simultaneously localize to the rear of a cell. Onsum and Rao (2007) proposed an antagonistic pathway model, in which PI3K were recruited by activated GPCRs to the membrane where their activity was further enhanced by $PI(3,4,5)P_3$; this resulted in a PI3K–$PI(3,4,5)P_3$ positive-feedback loop that aided in maintaining the cell front, whereas PTEN were simultaneously forced to the rear of a cell due to inhibition by F-actin. However, a considerable percentage of $PI(3,4,5)P_3$ molecules remained at the rear. This was inconsistent with experimental observations since the majority of $PI(3,4,5)P_3$ molecules localize to a cell front while only few are found at the rear (Dalous et al., 2008).

Another class of models was constructed based on the phase separation principle (Elson et al., 2010). Gamba et al. (2005) proposed a diffusion-limited phase separation model that mainly considered the regulation of PI3K/PTEN enzymatic activity and the diffusion of $PI(3,4,5)P_3$/$PI(4,5)P_2$. The competition between the ordering effect exerted by molecular interactions and the disordering effects exerted by molecular diffusivity induced instability of such a system toward a phase separation. However, according to this model, the characteristic times for phase separation varied from 5 to 60 min and were dependent on the GPCR activation levels. These simulated times were much longer than those experimentally observed, because cells are polarized within 180 s (Dalous et al., 2008; Weiner et al., 2002).

The reason why the models noted above fail to offer a full explanation of experimental data is conceptual rather than technical. Because it is a complex process, cell polarization is unlikely to be charged by a single mechanism. Based on this consideration, we temporarily put aside a longer-term goal of modeling polarization completely because this would require the entire signaling scheme from (I) to (IV) noted above. Our approach was based on the molecular mechanisms listed in (IV), which could allow us to restrict our attention to the question: how one common graded stimulus determines both the “forward” and “backward” response of a cell that is initially unpolarized (Cai and Devreotes, 2011; Franca-Koh and Devreotes, 2004; Parent, 2004)?

To justify this approach, we present a two-dimensional mathematical model for the polarization phase of eukaryotic chemotaxis by emphasizing polarization as a physical process that is shaped by bidirectional molecular transport. We let Rac serve as our starting point, and packed the molecular mechanisms in (IV) of the scheme noted previously into experimentally characterized PIs and Rac-mediated feedback loops (Lin et al., 2012; Weiner et al., 2002). We suggest that by assuming a static internal gradient of activated Rac derived from an external stimulus field, the spatial differences in Rac activation can be locally amplified via a short range Rac to $PI(3,4,5)P_3$ positive-feedback loop. This results in a persistent localization of PI3K and $PI(3,4,5)P_3$ and a simultaneous loss of PTEN membrane binding sites, $PI(4,5)P_2$, at the front of a cell. Therefore, a large number of PTEN dissociate from the front cell membrane, move to the cytosol, and after long range rearward diffusion, rebind with $PI(4,5)P_2$ at the rear of a cell. This closes