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Positioning of polarity formation by extracellular signaling during asymmetric cell division

Sungrim Seirin Lee

Department of Mathematical and Life Sciences, Hiroshima University, Kagamiyama 1-3-1, Higashi-hiroshima 739-8530, Japan

HIGHLIGHTS

- We explored the mechanism of polarity reversal in AP polarity formation using an extracellular signaling model.
- We found that a positive correlation between SRC-1 and the on-rate of PAR-2 is the essential mechanism underlying polarity reversal.
- The extracellular signal increases the robustness for the number of polarity pattern.
- We found the properties of the extracellular signal for inducing the robust polarity reversal.
- Mathematical basis was explored for the mechanism of polarity reversal.

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ABSTRACT

Anterior–posterior (AP) polarity formation of cell membrane proteins plays a crucial role in determining cell asymmetry, which ultimately generates cell diversity. In *Caenorhabditis elegans*, a single fertilized egg cell (P0), its daughter cell (P1), and the germline precursors (P2 and P3 cells) form two exclusive domains of different PAR proteins on the membrane along the anterior–posterior axis. However, the phenomenon of polarity reversal has been observed in which the axis of asymmetric cell division of the P2 and P3 cells is formed in an opposite manner to that of the P0 and P1 cells. The extracellular signal MES-1/SRC-1 has been shown to induce polarity reversal, but the detailed mechanism remains elusive. Here, using a mathematical model, I explore the mechanism by which MES-1/SRC-1 signaling can induce polarity reversal and ultimately affect the process of polarity formation. I show that a positive correlation between SRC-1 and the on-rate of PAR-2 is the essential mechanism underlying polarity reversal, providing a mathematical basis for the orientation of cell polarity patterns.

1. Introduction

Asymmetric cell division is one of the most widespread mechanisms for generating cell diversity. This occurs when a mother cell distributes its substrates asymmetrically before division, and then transfers them to two daughter cells. Consequently, the two daughter cells have different levels and types of substrates and thus do not show identical differentiation patterns. The mechanism of asymmetric cell division has been most well studied experimentally in the *Caenorhabditis elegans* embryo (Betschinger and Knoblich, 2004; Gönczy, 2005; Knoblich, 2008; Pruyne and Bretscher, 2000), and many mathematical models have been developed with the aim of understanding the mechanism leading to such asymmetric substrate distribution, with a particular focus on polarity formation in the membrane (Goehring et al. 2011a,b; Mori et al., 2008; Seirin Lee and Shibata, 2015; Tostevin and Howard, 2008). In *C. elegans*, a single fertilized egg cell (P0), its daughter cell (P1), and the germline precursors (P2 and P3 cells) are asymmetrically divided, forming two exclusive domains of different partitioning defective (PAR) proteins on the membrane (Fig. 1A). PAR-3/6 and PKC-3 proteins are distributed on the one side and PAR-1/2 and lethal giant larval-like 1 (LGL-1) are distributed on the other side, resulting in anterior–posterior (AP) polarity that determines the anterior–posterior axis. In a single cell, the process starts from a homogeneous state dominated by either the anterior or posterior side of the PAR protein, and then the other side of the PAR protein emerges. This results in the formation of exclusive anterior and posterior domains with a clear boundary that is maintained until cell cleavage starts. The first phase in which the other side of PAR protein begins to accumulate and spread is called the establishment phase, and the period in

E-mail addresses: seirin@hiroshima-u.ac.jp, seirin.lee@gmail.com

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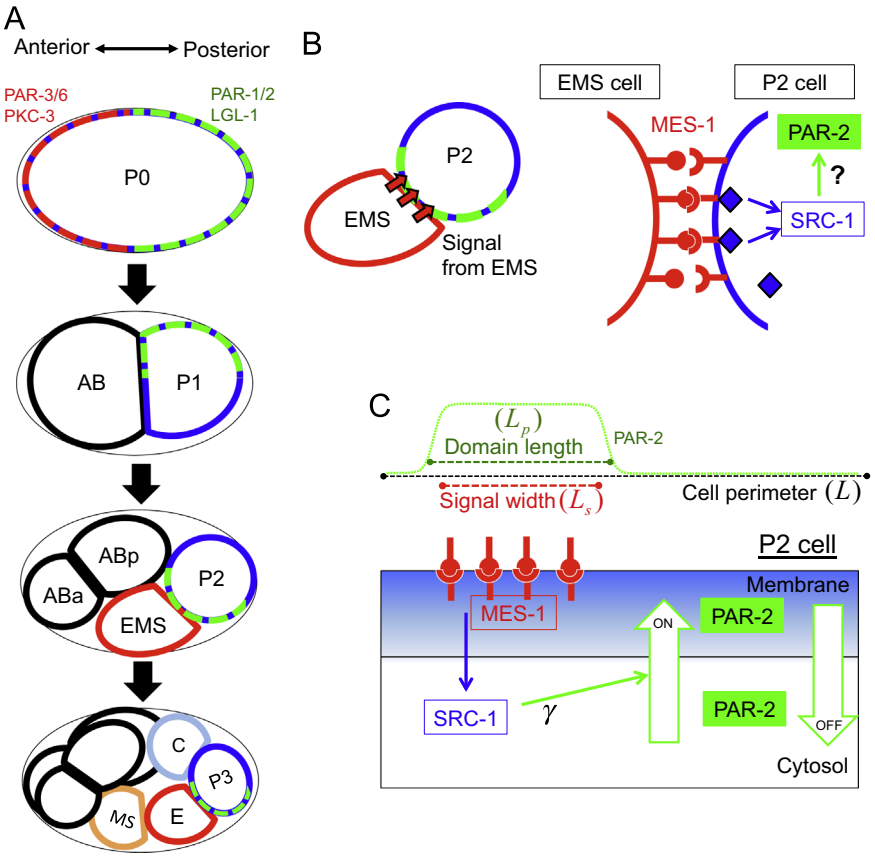

Fig. 1. Asymmetric division of the *C. elegans* embryo and modeling scheme. (A) The first to fifth stages of asymmetric division. The P0 zygote and germline cells (P1, P2, P3) are indicated in blue. P1, P2, and P3 cells are generated by the asymmetric divisions of P0, P1, and P2 cells, respectively, in which PAR-2 and PAR-6 show exclusive localization with a clear boundary (green and red dotted lines). During P0 and P1 cell division, PAR-2 is localized to one side and determines the posterior side, whereas in P2 and P3 cells, the PAR-2 domain is oriented toward the side of contact with the precursor cells EMS and E (red cells) (anterior side), respectively. (B) An extracellular signal is sent from the EMS cell to P2 cell by ligand-receptor binding of the transmembrane protein MES-1, and the signal ultimately activates the cytoplasmic protein SRC-1, either directly or indirectly, via an anonymous protein (blue squares). It is unknown precisely how SRC-1 affects the dynamics of PAR-2 (question mark). (C) Modeling scheme for determining the mechanism of PAR-2 localization and the effects of extracellular signals. The model was designed in one-dimensional space with cell perimeter L, and a periodic boundary condition. The signal width (i.e., the boundary width for contact between EMS and P2 cells) is denoted by L_s, and the length of the PAR-2 domain is denoted by L_p. It is assumed that the extracellular signal affects the on-rate of PAR-2 according to function $\gamma_{on}([S_C])$. (For interpretation of the references to color in this figure caption, the reader is referred to the web version of this paper.)

which the domain boundaries are determined is called the maintenance phase. The establishment phase lasts for approximately 2–8 min, followed by the maintenance phase, which lasts for another 16 min (Gönczy, 2005).

Interestingly, the axis of asymmetric cell division of P2 and P3 cells is formed opposite to that of P0 and P1 cells. This phenomenon is known as polarity reversal (Schierenberg, 1987), and extracellular signals play an important role in determining the orientation of the polarity pattern in the membrane (Arata et al., 2010; Siegrist and Doe, 2006). This polarity reversal allows for the P2 and P3 cells to generate the germline precursor daughter cells (P3 and P4 cells) in contact with endodermal precursors (EMS and E cells) (Arata et al., 2010; Gönczy, 2005). In the asymmetric divisions of P0 and P1 cells, the posterior/anterior side is determined by the location of the PAR-1/2 distribution/ PAR-3/6 distribution. During P2 and P3 cell divisions, PAR-1/2 protein is relocalized to a site opposite to that of PAR-1/2 distribution in P0 and P1 cells, i.e., the anterior side at the site of contact with the endodermal precursors (EMS and E cells), as shown in Fig. 1A.

The complete process of AP polarity formation is characterized by the following three mechanisms: membrane association and dissociation of proteins (Gönczy, 2005), diffusion into the membrane and cytosol (Goehring et al., 2011a), and active cortical and cytoplasmic flow induced by contraction of the acto-myosin cortex (Goehring et al., 2011b; Mayer et al., 2010; Niwayama et al., 2011). Seirin Lee and Shibata (2015) showed that AP polarity could be generated spontaneously at each step of the process, and the total mass of posterior protein and the difference in diffusion rates from the membrane to the cytosol were found to play important roles. They further found that flow could improve the sensitivity of the number of polarized PAR-2 domains to the initial perturbations, and the flow effect could always create a single polarity domain peak. However, robust positioning of the PAR-2 domain and the sensitivity of the domain positioning to either the initial perturbation (without flow), direction of flow, or the position for the initiation of acto-myosin contraction were not sufficient to explain the phenomenon of polarity reversal. This suggests that other mechanisms, in addition to those listed above, may be involved in the process of polarity reversal.

On the one hand, Arata et al. (2010) found that the orientation of PAR-2 protein localization in P2 and P3 cells is determined by an extracellular signal from the endodermal precursors, so that PAR-2 localization in the P2 cell is always established at the contact site with the endodermal precursor cell (EMS). They also demonstrated that joint signals from a transmembrane protein, MES-1, and an intracellular protein, SRC-1, play a critical role in determining the orientation for the asymmetric division of P2 cells. MES-1 has a dual function by sending extracellular signals from the endodermal precursor EMS, as well as receiving these signals in the P2 cell. SRC-1 then transduces this signal to control PAR-2 relocalization during polarity reversal in the P2 cell; however, the detailed mechanisms of this process are currently unknown (Fig. 1B). Mutation in either MES-1 or SRC-1 caused polarity