EXPERIMENTAL CELL RESEARCH 328 (2014) 258–266

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Review Article

PAR polarity: From complexity to design principles

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ARTICLE INFORMATION

Article Chronology:
Received 2 August 2014
Accepted 4 August 2014
Available online 14 August 2014

Keywords:
Cell polarity
Feedback
Networks
Modeling

ABSTRACT

The *par*-titioning-defective or PAR proteins comprise the core of an essential cell polarity network that underlies polarization in a wide variety of cell types and developmental contexts. The output of this network in nearly every case is the establishment of opposing and complementary membrane domains that define a cell's polarity axis. Yet, behind this simple pattern is a complex system of interactions, regulation and dynamic behaviors. How these various parts combine to generate polarized patterns of protein localization in cells is only beginning to become clear. This review, part of the Special Issue on Cell Polarity, aims to highlight several emerging themes and design principles that underlie the process of cell polarization by components of the PAR network.

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Introduction

The '*par*-titioning-defective' (PAR) proteins were discovered in pioneering genetic screens performed in *Caenorhabditis elegans* over 25 years ago. We now know that they comprise a conserved pathway that is essential for cell polarity throughout the animal kingdom. PAR proteins sit at major cellular crossroads, integrating upstream polarity cues and serving as spatial organizers for downstream pathways, including asymmetric transport, polarization of the cell cytoskeleton and trafficking pathways, and the

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http://dx.doi.org/10.1016/j.yexcr.2014.08.009
0014-4827/

segregation of cell fate determinants during asymmetric cell divisions [1–5].

Despite a large body of research documenting the molecules and molecular activities involved, a systems-level understanding of how a polarized pattern emerges from this molecular network remains beyond reach. This is in part due to complexity and variability of the PAR system, which complicates identification of core design principles. There are multiple sets of physical and regulatory interactions and several distinct 'PAR complexes.' Both the number and identity of molecular players can vary between cell type and organism, and in many cases there is functional redundancy. Given their central role in cellular organization, PAR proteins also interact with other cellular organizational systems including the cytoskeleton and endomembrane systems, which can potentially feed back onto the polarization process. Finally, while polarization can be viewed as a single cell phenomenon, in many contexts, the cell environment plays a key role, whether this be physical or chemical aspects of this environment, such as the basal lamina or contacts with neighboring cells [6,7].

Despite this complexity, it is important to note that in nearly all systems studied to date, it is the ability of PAR proteins to define discrete membrane domains that underlies the functional organization of the cell along the polarity axis. In addition, in most systems, this organization hinges on antagonistic interactions between various PAR components. Given these apparent universal features, a key goal going forward will be to distill core conserved features of the network that allow pattern formation, while at the same time trying to make sense of its inherent complexity. The past few years have seen significant progress on this front. Additional components continue to be identified. New details have emerged regarding interactions between PAR components. We have begun to define the mobility and dynamic behavior of PAR components in cells. And the regulatory mechanisms that modulate PAR activity are becoming more clear. Alongside these new results, there is increased interest in the application of theory and modeling to help identify emergent properties and design principles of these complex networks.

Given the limited scope of this review, I will not seek to comprehensively address detailed molecular mechanisms. Rather, given the context of this special issue on polarity, I will try to address a few emerging themes that simultaneously highlight core features of the PAR system as well as its complexity, chiefly focusing on feedback and cross-regulation, balancing PAR protein amounts and activity, PAR protein mobility and dynamics, as well as recent theoretical analysis that has attempted to bring these ideas together into a coherent, quantitative framework.

The PAR network

Core components of the PAR network include the kinases, PAR-1 and aPKC, the 14-3-3 protein PAR-5, which binds phosphorylated substrates, the PDZ-containing scaffold proteins PAR-3/Bazooka and PAR-6, the small Rho-family GTPase CDC-42, and Lethal Giant Larva (LGL). There are also a number of context-specific players. In the *C. elegans* embryo, the RING-finger containing protein, PAR-2 plays an essential role in anterior–posterior polarization and polarization of the germ lineage, where it acts together with PAR-1. In epithelia, one finds the additional involvement of the apical Crumbs-Pals1-PatJ complex and the basolateral proteins DLG-1 and Scribble, as well as a number of other PAR regulators that include Yurt and Slmb [8–10]. This list is by no means exhaustive and I encourage interested readers to consult a variety of excellent recent reviews [1–5].

At a coarse-grained level, we can consider these components to fall broadly into antagonistic groups that demarcate the cell membrane into polarity domains (Fig. 1A). In the *C. elegans* embryo, as well as the *Drosophila* oocyte and neuroblasts, PAR-3/PAR-6/aPKC co-segregate to one cell half and exclude PAR-1 and LGL (and PAR-2 in *C. elegans*). PAR-1, LGL, and PAR-2 co-segregate to the other cell half and reciprocally exclude PAR-3/PAR-6/aPKC. PAR-5 is localized throughout the cytoplasm and is thought to act throughout the cell to modulate the activity of diverse phosphorylated substrates, including PAR proteins.

Current data support a complex web of interactions between these various proteins (Fig. 1D). The core players PAR-3/PAR-6/aPKC co-purify. However, in most contexts they only partially co-localize, suggesting that the three proteins do not form a constitutive complex [11–13]. CDC-42 can bind PAR-6 and is required to maintain PAR-6/aPKC at the cell membrane [14,15]. PAR-1 and PAR-2 appear to interact [16], however, there is no evidence that either interacts with LGL. Instead, LGL co-purifies with its antagonists PAR-6 and aPKC [17,18].

In epithelia, the picture is complicated by additional players, including the apical Crumbs(Crb)–Stardust(Sdt)–Pals1 complex, which associates with PAR-6/aPKC, and Scribbled (Scr) and Discs Large (Dlg), which colocalize with LGL and PAR-1 at basolateral membranes (Fig. 1B). In these cells, PAR-3 localizes primarily to the junctions, defining an additional junctional region. Nonetheless, the overall theme is similar to non-epithelia: aPKC, as part of the Crumbs complex, excludes basolateral proteins from the apical domain, while LGL/Scr/Dlg exclude PAR-6/aPKC containing complexes, perhaps through preventing PAR-6/aPKC from associating with other apical components such as Crb and PAR-3 [2]. There appears to be an additional level of cross-talk between PAR-3- and Crb-containing complexes to ensure that PAR-3 and Crb localize to distinct regions in the apico-junctional domain [13,19].

Feedback

We have already seen that a central feature of the PAR polarity network is mutual exclusion between PAR-6/aPKC containing complexes on one hand, and variously PAR-1, PAR-2 and LGL on the other. Intuitively, this mutual exclusion helps explain their anti-symmetric localization in the cell. For example, in the *C. elegans* zygote, phosphorylation of PAR-1, PAR-2 and LGL by asymmetrically localized aPKC is thought to exclude them from the anterior membrane. In support of this model, loss of PAR-3, PAR-6, aPKC or CDC-42 results in enrichment of PAR-1, PAR-2, and LGL throughout the cell membrane. Conversely, loss of PAR-1 or PAR-2 leads to aberrant spreading of PAR-3, PAR-6, and aPKC, which are thought to be excluded through the PAR-1-dependent phosphorylation of PAR-3 (recently reviewed in [1,20]). PAR-5/14-3-3 has been directly implicated in moderating this antagonism. By binding these phosphorylated substrates, PAR-5 can displace or sequester them from membranes [21–23]. The activity of LGL remains poorly understood, but likely involves its ability to displace PAR-3 from the PAR-3/PAR-6/aPKC complexes and inhibit aPKC activity [17,24].