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Review article

Polarity in plant asymmetric cell division: Division orientation and cell fate differentiation

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ABSTRACT

Asymmetric cell division (ACD) is universally required for the development of multicellular organisms. Unlike animal cells, plant cells have a rigid cellulosic extracellular matrix, the cell wall, which provides physical support and forms communication routes. This fundamental difference leads to some unique mechanisms in plants for generating asymmetries during cell division. However, plants also utilize intrinsically polarized proteins to regulate asymmetric signaling and cell division, a strategy similar to the differentiation mechanism found in animals. Current progress suggests that common regulatory modes, i.e. protein spontaneous clustering and cytoskeleton reorganization, underlie protein polarization in both animal and plant cells. Despite these commonalities, it is important to note that intrinsic mechanisms in plants are heavily influenced by extrinsic cues. To control physical asymmetry in cell division, although our understanding is fragmentary thus far, plants might have evolved novel polarization strategies to orientate cell division plane. Recent studies also suggest that the phytohormone auxin, one of the most pivotal small molecules in plant development, regulates ACD in plants.

Contents

1. Introduction

Asymmetric cell divisions (ACDs) are imperative for multicellular organisms to generate diversified cell types, while maintaining self-renewal stem cell pools (Abrash and Bergmann, 2009; Knoblich, 2008). Both intrinsic and extrinsic factors cause

Abbreviations: ACD, asymmetric cell division; PM, plasma membrane; MT, microtubule; F-actin, filamentous actin; M, meristemoid; SLGC, stomatal lineage ground cell; GC, guard cell; SMC, subsidiary mother cell

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asymmetries during cell division. Intrinsic mechanisms refer to those of which cell fate differentiation occurs prior to cytokinesis of the parental cell (Goldstein and Macara, 2007; Knoblich, 2008). Extrinsic factors drive differentiation outcome by asymmetric placement of the daughter cells into two distinct microenvironments (Fuller and Spradling, 2007). While both processes are important in complex organisms, intrinsic or extrinsic may have more weight over the other under certain conditions.

"Cell polarization", or "symmetry breaking", describes spontaneous assembly of cell cortical membrane domains. During this process proteins, mRNAs, organelles, cytoskeletal components among other molecules become distributed unevenly. Polarization occurs in essentially all cellular organisms and is required for fundamental processes in morphogenesis, cell division as well as cell differentiation (Freisinger et al., 2013; Yang and Lavagi, 2012). Cell polarization is a typical intrinsic regulatory measure that is required early in an ACD and is significant for subsequent checkpoints, e.g. mitotic spindle alignment, division plane positioning and daughter cell fate specification. The molecular mechanisms underpinning stem cell ACD have been described in model systems, such as the worm *C. elegans* embryos, the fruit fly *Drosophila melanogaster* nervous systems, and the budding yeast *Saccharomyces cerevisiae* (Inaba and Yamashita, 2012). In higher plants, the key roles of cell polarization in stem cell ACD are manifested by asymmetrically distributed proteins and signaling pathways. Contrary to the dominant roles of animal polarity proteins being almost entirely intrinsic cues, plant polarity proteins seem to participate in both intrinsic and extrinsic pathways to regulate divisional asymmetries in development. In addition, the phytohormone auxin is recognized as an important regulator of ACD in multiple developmental contexts (Balcerowicz et al., 2014; Le et al., 2014; Zhang et al., 2014). This review mainly focuses on the current understanding of how ACD participating proteins and related signaling pathways are asymmetrically distributed in plant cells and how auxin activity in addition to these pathways may regulate physical asymmetry and differential identity in cell division. Other mechanisms underlying cell fate asymmetry in plant ACD, but not necessarily associated with cell physical asymmetry, have been discussed previously (Abrash and Bergmann, 2009; Fisher and Sozzani, 2016; Petricka et al., 2009; Pillitteri et al., 2016; Ten Hove and Heidstra, 2008; Wu and Gallagher, 2011).

2. Symmetry breaking at the cortical membrane

Hallmark polarity proteins in animals, e.g. the Cdc42 small GTPase (Chant, 1999; Slaughter et al., 2009) and PAR proteins (Goldstein and Macara, 2007; Nance and Zallen, 2011), have been investigated intensively for the past decades. However, many of these highly conserved proteins found in animals are missing from the plant genome. The discoveries of polarized proteins in higher plants, e.g. the PANGLOSS (PAN) receptor-like proteins and the plant-specific, novel protein BREAKING OF ASYMMETRY IN THE STOMATAL LINEAGE (BASL) that participate in the regulation of plant ACD, have not been made until a few years ago (Cartwright et al., 2009; Dong et al., 2009). But excitingly, recent progress disclosed new genetic and physical partners in the PAN-mediated pathway (Humphries et al., 2011; Zhang et al., 2012; Facette et al., 2015) and BASL-centered polarity system (Pillitteri et al., 2011; Zhang et al., 2015). Current data suggest that, despite these polarity proteins being plant-specific, common regulatory themes, such as positive feedback loops, cytoskeletal reorganization and spatially organized cell signaling, underpin the cell polarity-driven ACD in both animals and plants.

2.1. Protein polarization: positive feedback loops

The yeast *S. cerevisiae* is a single-celled organism that continuously produces small daughter cells *via* polarizing the mother cell to form a bud, which expands and detaches from the mother. Polarization of the mother cells can be easily recognized as a patch of enriched cytoskeleton and membrane trafficking components at the polarity site, which promote the growth of the daughter cell. The polarity regulator, small Rho GTPase Cdc42, was first identified by Adams and others (Adams et al., 1990) and later established as "the center of cell polarization" ubiquitously from yeast to humans (Etienne-Manneville, 2004; Park and Bi, 2007). Loss of Cdc42 function leads to polarization failure of the mother cell and causes division problems (Adams et al., 1990). The cycling of Cdc42 between active guanosine triphosphate (GTP)-bound and inactive guanosine diphosphate (GDP)-bound forms is controlled by orchestrated activity of activators (guanine nucleotide exchange factors, GEFs), inhibitors (ATPase-activating proteins, GAPs) and other modulators (Rho GTPase-dissociation inhibitors, GDIs) (Vetter and Wittinghofer, 2001). One of the two major pathways that distribute Cdc42 to a highly polarized fashion at the cell cortex is actin-independent and requires a Cdc42-Bem1-Cdc24 centered positive feedback loop (Fig. 1). Bem1 is a scaffold protein and Cdc24 is a GEF activator of Cdc42. In the absence of any spatial cues, stochastically activated Cdc42 molecules may spontaneously cluster to initiate a cortical site where Bem1 is recruited, which locally accumulates Cdc24 that further activates Cdc42 to expand the polarity domain (Butty et al., 2002; Smith et al., 2013). More recently, a Cdc42 effector p21-activated kinase PAK was also found as a part of the complex that binds to Cdc24 and contributes to spontaneous polarization of yeast cells (Kozubowski et al., 2008; Woods et al., 2015). Thus, positive feedback loops provide a base for spontaneous initiation of Cdc42 polarization.

In *Arabidopsis*, the stomatal lineage cells divide asymmetrically to produce highly specialized guard cells that conduct gas exchange between the plant and the atmosphere (Bergmann and Sack, 2007). The initiation of stomatal precursor cells occurs in young developing leaves and their division orientation appears random relative to the leaf axis (Lau and Bergmann, 2012), suggesting an intrinsic polarization property of the cells. This is strongly supported by the discovery of the plant-specific *BASL* gene (Dong et al., 2009). In the absence of *BASL*, the stomatal lineage cells lost their full capacity to divide asymmetrically, thus producing an enlarged proliferating population with equal division pattern and disturbed daughter cell fate segregation (Dong et al., 2009). The localization of BASL protein is mainly featured by its strong polar accumulation at the cell cortex that is indispensible for its function (Dong et al., 2009). In plant cells, the molecular mechanisms for protein polarization are better understood for PIN-FORMED (PIN) auxin transports. PINs are membrane integral proteins and often occupy distinct plasma membrane domains in *Arabidopsis* plants (Friml, 2003). PIN polar targeting and maintenance at the plasma membrane involve rapid and constitutive vesicular recycling between the PM and the endosomes (Feraru and Friml, 2008; Grunewald and Friml, 2010).

How the non-membrane protein BASL polarizes and associates to the PM remains unknown, but interestingly, both positive feedback loop and protein spontaneous clustering appear to be part of the process (Fig. 1). The positive feedback loop involves BASL, the Mitogen Activated Protein Kinase (MAPK) Kinase Kinase YODA (YDA) and MAPK 3 and 6 (MPK3/6), both of which are pivotal signaling molecules in stomatal development (Bergmann et al., 2004; Wang et al., 2007). Activation of BASL polarization can be mediated by MPK3/6 phosphorylation, which promotes nuclear export and cortical polar accumulation (Zhang et al., 2015). At the cell cortex, phosphorylated BASL functions as a scaffold protein