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Review

Phosphoinositides: Lipids with informative heads and mastermind functions in cell division ☆

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ABSTRACT

Phosphoinositides are low abundant but essential phospholipids in eukaryotic cells and refer to phosphatidylinositol and its seven polyphospho-derivatives. In this review, we summarize our current knowledge on phosphoinositides in multiple aspects of cell division in animal cells, including mitotic cell rounding, longitudinal cell elongation, cytokinesis furrow ingression, intercellular bridge abscission and post-cytokinesis events. PtdIns(4,5)P_2 production plays critical roles in spindle orientation, mitotic cell shape and bridge stability after furrow ingression by recruiting force generator complexes and numerous cytoskeleton binding proteins. Later, PtdIns(4,5)P_2 hydrolysis and PtdIns3*P* production are essential for normal cytokinesis abscission. Finally, emerging functions of PtdIns3*P* and likely PtdIns(4,5)P_2 have recently been reported for midbody remnant clearance after abscission. We describe how the multiple functions of phosphoinositides in cell division reflect their distinct roles in local recruitment of protein complexes, membrane traffic and cytoskeleton remodeling. This article is part of a Special Issue entitled Phosphoinositides.

1. Introduction

Animal cell division is driven by dramatic cell shape changes. Each step of cell division relies on cytoskeleton and lipid remodeling, local recruitment of protein complexes and membrane trafficking. One of the best examples of such interplay occurs during cytokinesis, which leads to the physical separation of the daughter cells and concludes cell division [1–7]. The contraction of the cytokinesis furrow at the equator of the spindle takes place in anaphase and is driven by the acto-myosin cytoskeleton, which is tightly coupled to the plasma membrane. After furrow ingression, the stability of the intercellular bridge connecting the daughter cells depends on other cytoskeleton elements such as septins and Anillin. Finally, the bridge is cut by the activity of the ESCRT (Endosomal Sorting Complex Required for Transport) filamentous cytoskeleton, which likely triggers abscission [4,6,7]. This abscission machinery assembles on the side of the midbody, the central part of the intercellular bridge [8], and ultimately drives the fusion of the plasma membrane in a zone free from actin and microtubules. The orientation of the cytokinesis plane is defined by the position of the mitotic spindle, which is established earlier during cell division in prometaphase and metaphase [9–11]. The orientation of the cell division axis is particularly important during oriented cell divisions, which are essential for embryogenesis and adult tissue homeostasis. Spindle orientation and positioning again depend on a complex dialogue between spindle microtubules, the mitotic actin cortex and membrane lipids.

In this review, we detail the role of phosphoinositides in animal cell division. Several in-depth reviews have focused on the role of phosphoinositides in cytokinesis [12–17] and we highlight the latest findings in this growing field. We also provide the first review on the role of phosphoinositides in other, less documented, but exciting aspects of cell division, namely spindle orientation, mitotic cell shape, cell rounding and post-cytokinesis events.

Although they represent less than 1% of total cellular lipids, phosphoinositides (PIs) are essential phospholipids in eukaryotic cells and are essentially found on the cytoplasmic leaflet of cellular

Abbreviations: DAG, diacylglycerol; ERM, Ezrin, Radixin, Moesin; ESCRT, Endosomal Sorting Complex Required for Transport; Ins(1,4,5)P_3, inositol 1,4,5-trisphosphate; LGN, Leucine–Glycine–Asparagine repeat protein; MBR, midbody remnant; NuMA, Nuclear Mitotic Apparatus protein; OCRL, Oculo-Cerebro-Renal syndrome of Lowe; PITP, phosphatidylinositol transfer protein; PIs, phosphoinositides. This generic term refers collectively to PtdIns and the seven polyphosphoinositides [PtdIns3*P*, PtdIns4*P*, PtdIns5*P*, PtdIns(4,5)P_2, PtdIns(3,5)P_2, PtdIns(3,4)P_2, PtdIns(3,4,5)P_3]; PLC, phospholipase C; PtdIns, phosphatidylinositol or 1-(3-*sn*-Phosphatidyl)-D-*myo*-inositol; PtdIns3*P*, phosphatidylinositol 3-monophosphate; PtdIns4*P*, phosphatidylinositol 4-monophosphate; PtdIns5*P*, phosphatidylinositol 5-monophosphate; PtdIns(4,5)P_2, phosphatidylinositol 4,5-bisphosphate; PtdIns(3,5)P_2, phosphatidylinositol 3,5-bisphosphate; PtdIns(3,4)P_2, phosphatidylinositol 3,4-bisphosphate; PtdIns(3,4,5)P_3, phosphatidylinositol 3,4,5-trisphosphate; PTEN, phosphatase and tensin homologue deleted on chromosome 10; RhoGEF, Rho Guanine nucleotide Exchange Factor

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membranes [18–21]. In this review, we use the term PIs in its broad acceptance to collectively refer to phosphatidylinositol (PtdIns) and phosphorylated derivatives. Seven polyphosphoinositides [PtdIns3*P*, PtdIns4*P*, PtdIns5*P*, PtdIns(4,5)P_2, PtdIns(3,5)P_2, PtdIns(3,4)P_2, PtdIns(3,4,5)P_3] indeed result from the reversible phosphorylation of hydroxyl positions 3, 4 and 5 of the *myo*-inositol headgroup of phosphatidylinositol. The hydrophilic head of PIs is exposed to the cytosol and is modified by selective PI-kinases and PI-phosphatases (Fig. 1). As these enzymes are themselves highly regulated in space and time, specific PI membrane domains are dynamically generated at the surface of the plasma membrane and intracellular compartments, and thus contribute to compartment identity. Importantly, particular PI functions are achieved by the recruitment of specific PI-binding modules selective for one or a few PIs (e.g. PH binding to PtdIns(4,5)P_2 or FYVE binding to PtdIns3*P*) ([22,23] and Balla et al. *review in this issue*).

To date, several PIs have been implicated in cell division, although not necessarily in all animal species: PtdIns, PtdIns3*P*, PtdIns4*P*, PtdIns(4,5)P_2, and PtdIns(3,4,5)P_3 (Figs. 1 and 2). We describe how this has been established, which PI-modifying enzymes are involved and how PIs control the recruitment of specific proteins that could explain their function in each step of cell division.

2. Phosphoinositide functions in mitotic spindle orientation

Spindle orientation determines the axis of cell division and depends on force generator complexes localized at the mitotic cell cortex, which ultimately enable proper interactions with spindle microtubules. In animal cells, the evolutionary-conserved complex Gαi/LGN/NuMA recruits the dynein motor that is believed to pull on astral microtubules and direct spindle rotation [9–11]. An emerging concept is that PIs play multiple roles in the polarized recruitment of LGN/NuMA at the mitotic cell cortex and thus contribute to specific spindle orientation parallel to the substratum and within the horizontal plane (Figs. 1 and 2).

2.1. PtdIns(3,4,5)P_3 and planar orientation of the spindle

The first hint that PIs have an instructive role in spindle orientation came from a study in non-polarized HeLa cells [24]. The Akt-PH-GFP probe reveals an intriguing belt of PtdIns(3,4,5)P_3 at the mitotic cortex, within the midsection of prometaphase, metaphase and anaphase cells (Fig. 3A, left). Pharmacological inhibition of PI 3-kinases leads to spindle orientation defects (instead of being parallel to the substratum, spindles are tilted in the Z-axis) and is associated with a reduction of the PtdIns(3,4,5)P_3 localization to the cortex. Importantly, the spindle orientation defects are partially rescued by exogenous addition of PtdIns(3,4,5)P_3 but not PtdIns(3,4)P_2 or PtdIns(4,5)P_2. Conversely, depletion of PTEN (which converts PtdIns(3,4,5)P_3 into PtdIns(4,5)P_2, Fig. 1) causes expansion of the PtdIns(3,4,5)P_3 domain over the whole cortex and is also associated with spindle orientation defects. Interestingly, both lack and excess of PtdIns(3,4,5)P_3 result in the mislocalization of the dynein-associated dynactin, that is dispersed throughout the cortex rather than being enriched in the cortical midsection, as observed in normal mitotic cells. Thus the correct levels of PtdIns(3,4,5)P_3 are important for spindle orientation parallel to the substratum by restricting the localization of force generators (Fig. 3A).

2.2. PtdIns(4,5)P_2 function in spindle positioning and orientation within the horizontal plane

Two lines of evidence demonstrate that PtdIns(4,5)P_2 also plays a crucial role in spindle positioning and orientation in *Caenorhabditis elegans* and in mammalian cells. The first cell division of *C. elegans* embryo is asymmetric. Asymmetry results from the positioning of the mitotic spindle closer to the posterior pole through the asymmetric localization or activity of the Gαi(GOA-1/GOA-16)/LGN(GPR1/2)/NuMA(LIN-5)/dynein complex at the posterior cortex [9,11]. The PAR polarity proteins also control spindle positioning, but how they are connected to the Gαi/LGN/NuMA/dynein complex was unknown. Interestingly, PAR proteins are required for restricting the localization of the PtdIns4*P*-5 kinase PPK-1 specifically to the posterior cortex [25]. In addition, depletion of PPK-1 results in abnormally low levels of LGN at the cortex and decreased spindle pulling forces. Conversely, in a situation in which PPK-1 is uniformly localized LGN/NuMA becomes symmetrically associated with the cortex and this leads to increased pulling forces on the spindle. Thus it has been proposed that the asymmetric localization of PtdIns(4,5)P_2 by PPK-1 directs the posterior localization of LGN/NuMA, leading to posterior spindle displacement [25]. Two important questions are raised by this pioneer study: first, whether not only is the PtdIns4*P* 5-kinase but also PtdIns(4,5)P_2 asymmetrically

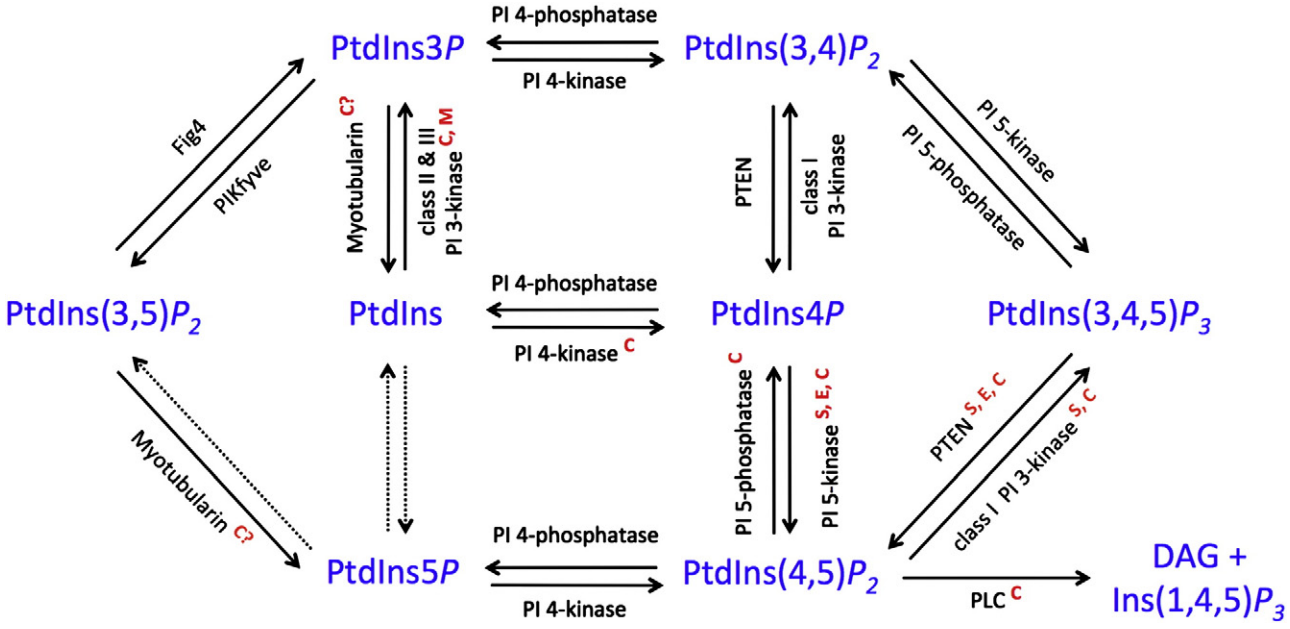

Fig. 1. Enzymes involved in phosphoinositide interconversion and their role in cell division. Kinases and phosphatases required for spindle orientation (S), mitotic cell rounding and elongation (E), cytokinesis (C) and midbody clearance (M) are indicated.