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Review

Phosphoinositide phosphatases in cell biology and disease

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ABSTRACT

Phosphoinositides are essential signaling molecules linked to a diverse array of cellular processes in eukaryotic cells. The metabolic interconversions of these phospholipids are subject to exquisite spatial and temporal regulation executed by arrays of phosphatidylinositol (PtdIns) and phosphoinositide-metabolizing enzymes. These include PtdIns- and phosphoinositide-kinases that drive phosphoinositide synthesis, and phospholipases and phosphatases that regulate phosphoinositide degradation. In the past decade, phosphoinositide phosphatases have emerged as topics of particular interest. This interest is driven by the recent appreciation that these enzymes represent primary mechanisms for phosphoinositide degradation, and because of their ever-increasing connections with human diseases. Herein, we review the biochemical properties of six major phosphoinositide phosphatases, the functional involvements of these enzymes in regulating phosphoinositide metabolism, the pathologies that arise from functional derangements of individual phosphatases, and recent ideas concerning the involvements of phosphoinositide phosphatases in membrane traffic control.

Contents

1. Introduction

Phosphoinositides are phosphorylated derivatives of PtdIns (Fig. 1), and these lipid species represent quantitatively minor components of cell membranes. In eukaryotic cells, PtdIns generally constitutes less than 10% of the total cellular phospholipid while phosphoinositides usually comprise only several percent of total cellular inositol lipids [163,59,130,39,113]. However, in spite of their low abundance, phosphoinositides regulate a host of fundamental cellular processes. These include signal transduction, intracellular membrane trafficking, cytoskeleton remodeling, nuclear events, control of cell growth and survival, etc. This functional diversity of function in part reflects the molecular diversity of these compounds. Mammalian cells produce seven chemically distinct, but interconvertible, phosphoinositide species: phosphatidylinositol 3-phosphate (PtdIns-3-P), PtdIns-4-P, PtdIns-5-P, phosphatidylinositol 3,5-bisphosphate (PtdIns-3,5-P_2), PtdIns-4,5-P_2,

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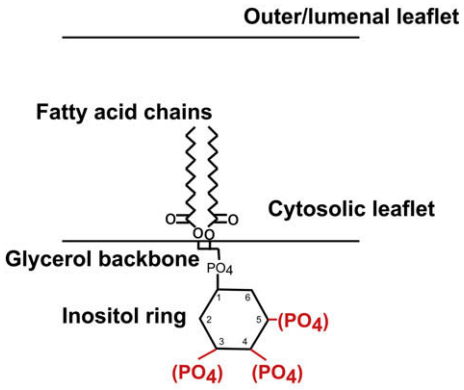

Fig. 1. Phosphoinositides are phosphorylated derivatives of PtdIns. The chemical structures of PtdIns and Phosphoinosities are shown highlighting the inositol headgroup, glycerol backbone and two fatty acyl chains. The inositol headgroup can be combinatorially phosphorylated at the D-3OH, -4OH, -5OH positions of the inositol ring as indicated in red.

PtdIns-3,4-P_2, and phosphatidylinositol-3,4,5-trisphosphate (PtdIns-3,4,5-P_3) (Fig. 1). Phosphoinositides phosphorylated at the 3-OH position are not substrates for phospholipases C, so these phosphoinositides hold intrinsic signaling functions whose execution is not mediated through the action of derivative second messengers. It is through the action of phosphatases that 3-OH phosphoinositides are degraded.

Yeast produce five phosphoinositide species (Fig. 2), and lack the capacity to generate the PtdIns-3,4-P_2 and PtdIns-3,4,5-P_3 species produced by mammals and other higher eukaryotes (Fig. 3). The 3-OH and 4-OH PtdIns-monophosphate species represent the major phosphoinositides in yeast, each constituting ca. 1.5% of total inositol glycerophospholipid in this organism (ca. 0.3% of total glycerophospholipid). PtdIns-4,5-P_2 is present at approximately half the mass of PtdIns-3-P or PtdIns-4-P. Basal PtdIns-3,5-P_2 levels are vanishingly low, essentially at the level of detection, until yeast are subject to stress – particularly hyperosmotic stress [43]. Upon such challenge, PtdIns-3,5-P_2 levels rise rapidly. The 4-OH phosphoinositides are all essential in yeast as evidenced by demonstrations that functional ablation of either one of the two major PtdIns 4-OH kinases (Pik1 and Stt4), or of the single PtdIns-4-P 5-OH kinase (Mss4), represent lethal events. Although 3-OH phosphoinositides play important homeostatic functions in yeast, these are essential for cell viability only under stress conditions [177,59,130].

Of the total inositol lipid content in mammalian cells, approximately 5% is invested in PtdIns-4-P and PtdIns-4,5-P_2, respectively – i.e. 0.5% of total cellular phospholipid in each case [162]. These two 4-OH phosphorylated phosphoinositides represent by far the major phosphoinositide species in mammalian cells, constituting 90% of total cellular phosphoinositides [170,39]. By comparison, less than 0.25% of the total inositol phospholipid is phosphorylated on the D-3 position – PtdIns-3-P represents only some 0.04% of total membrane phospholipid [59,130,218,170,213,39].

The chemically distinct phosphoinositide species each execute unique functions in cells, and the mono-phosphorylated phosphoinositides are not simple intermediates in production of the higher poly-phosphorylated species. Translation of chemical diversity to functional diversity is in part determined by preferred interface of individual phosphoinositide species with regulatory effector proteins that harbor phosphoinositide -binding domains. Examples include the pleckstrin homology (PH) domains, phox homology (PX) domains, epsin N-terminal homology (ENTH) domains, band 4.1/ezrin/radixin/moesin (FERM) and Fab1p/YOTB/Vac1p/EEA1 (FYVE) domains and lysine–arginine patches [39,104].

All phosphoinositides are restricted to the cytosolic leaflets of intracellular membranes, and these are not homogeneously distributed in the membranes that contain them [170]. Moreover, the representation of individual phosphoinositide species varies between subcellular compartments and contributes to establishment and/or maintenance of organelle identity. For example, PtdIns-3-P is enriched on endocytic membranes, PtdIns-4-P on *trans*-Golgi (TGN) membranes, and PtdIns-4,5-P_2 is localized primarily on the plasma membrane – although Golgi pools are detected. PtdIns-3,5-P_2 is most abundant in multivesicular bodies (MVBs) and late endosomes, on the yeast vacuole, and on mammalian lysosomes [31,206,109,35,36,39]. PtdIns-3,4,5-P_3 is produced almost exclusively on the inner leaflet of the plasma membrane, although this most highly modified phosphoinositide might also accumulate on membranes of intracellular organelles and in the nuclear matrix following growth factor receptor activation [48,179,102,203,214,213].

Steady-state phosphoinositide distribution is the manifestation of a highly dynamic program of production and turnover executed

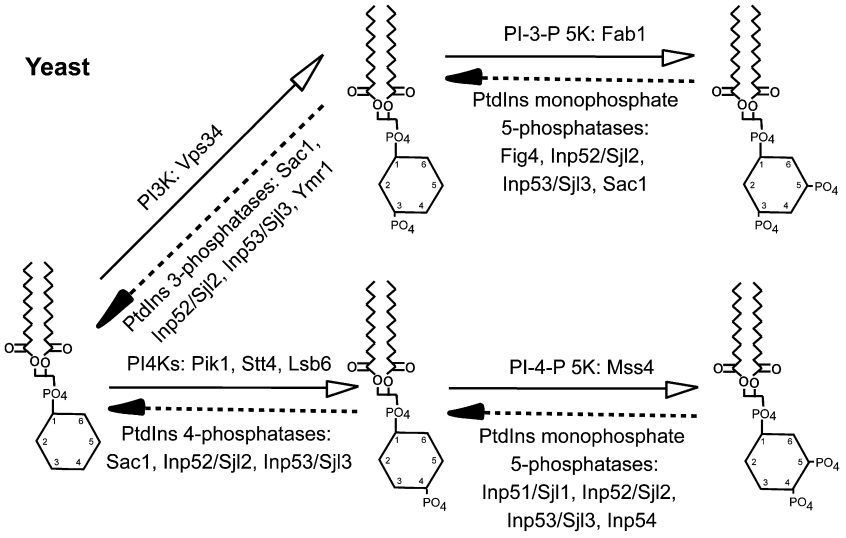

Fig. 2. Phosphoinositide metabolism in the yeast *Saccharomyces cerevisiae*. The execution points of the yeast PtdIns kinases and phosphoinositide phosphatases that regulate the synthesis and turnover of phosphoinositides, respectively, are identified.