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Cellular and molecular interactions of phosphoinositides and peripheral proteins

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ABSTRACT

Anionic lipids act as signals for the recruitment of proteins containing cationic clusters to biological membranes. A family of anionic lipids known as the phosphoinositides (PIPs) are low in abundance, yet play a critical role in recruitment of peripheral proteins to the membrane interface. PIPs are mono-, bis-, or trisphosphorylated derivatives of phosphatidylinositol (PI) yielding seven species with different structure and anionic charge. The differential spatial distribution and temporal appearance of PIPs is key to their role in communicating information to target proteins. Selective recognition of PIPs came into play with the discovery that the substrate of protein kinase C termed pleckstrin possessed the first PIP binding region termed the pleckstrin homology (PH) domain. Since the discovery of the PH domain, more than ten PIP binding domains have been identified including PH, ENTH, FYVE, PX, and C2 domains. Representative examples of each of these domains have been thoroughly characterized to understand how they coordinate PIP headgroups in membranes, translocate to specific membrane docking sites in the cell, and function to regulate the activity of their full-length proteins. In addition, a number of novel mechanisms of PIP-mediated membrane association have emerged, such as coincidence detection–specificity for two distinct lipid headgroups. Other PIP-binding domains may also harbor selectivity for a membrane physical property such as charge or membrane curvature. This review summarizes the current understanding of the cellular distribution of PIPs and their molecular interaction with peripheral proteins.

1. Phosphoinositides

Cellular lipid membranes are dynamic structures that contain >1000 different lipid species (van Meer, 2005). This dynamic variety of lipids, which includes the phosphoinositides (PIPs)[1], provides spatial and temporal signals to mediate and direct interactions with target proteins. PIPs are derived from phosphatidylinositol (PI), synthesized in the ER by a PI synthase enzyme, which utilizes CDP-diacylglycerol (DAG) and *myo*-inositol (Agranoff et al., 1958). PI is then transported from the ER by PI transfer proteins (Cockcroft and Carvou, 2007; Ile et al., 2010) and possibly vesicular trafficking to different cellular membranes. Recently, the PI synthase enzyme was found localized in a highly mobile organelle originating from the ER (Kim et al., 2011). The discovery of this organelle harboring PI synthase suggests PI may be dynamically disseminated throughout the cell via this machinery.

Once PI is distributed it can be reversibly phosphorylated on the 3, 4, and/or 5 hydroxyl group yielding seven different PIP species (Figs. 1 and 2). These include the monophosphorylated (PI(3)P, PI(4)P, and PI(5)P) as well as the bis (PI(3,4)P_2, PI(3,5)P_2, and PI(4,5)P_2) and trisphosphorylated (PI(3,4,5)P_3) forms (Fig. 2). PI can vary from ~10 to 20 mol% of total lipid in different cells and tissues (Nasuhoglu et al., 2002; Wenk et al., 2003) while phosphorylated PIPs make up less than 1% of the total cellular lipid pool. Despite such low cellular concentrations of PIPs they

Abbreviations: ANTH, AP180 amino-terminal homology; BAR, Bin amphiphysin Rvs (BAR); C2, protein kinase C conserved 2; ENTH, epsin amino-terminal homology; FAPP1, four-phosphate adaptor protein 1; FERM, band 4.1, ezrin, radixin, moesin; FYVE, Fab1, YOTB, Vac1, and EEA1; GOLPH3, Golgi phosphoprotein 3; KA1, kinase associated-1 domains; MIL, membrane insertion loop; PA, phosphatidic acid; PDZ, postsynaptic density 95, disk large, zonula occludens; PH, pleckstrin homology domain; PI, phosphatidylinositol; PIP, phosphoinositide; PKC, protein kinase C; Protein Data Bank, PDB; PM, plasma membrane; PS, phosphatidylserine; PTB, phosphotyrosine binding (PTB); PX, Phox domain; TGN, trans-Golgi network.

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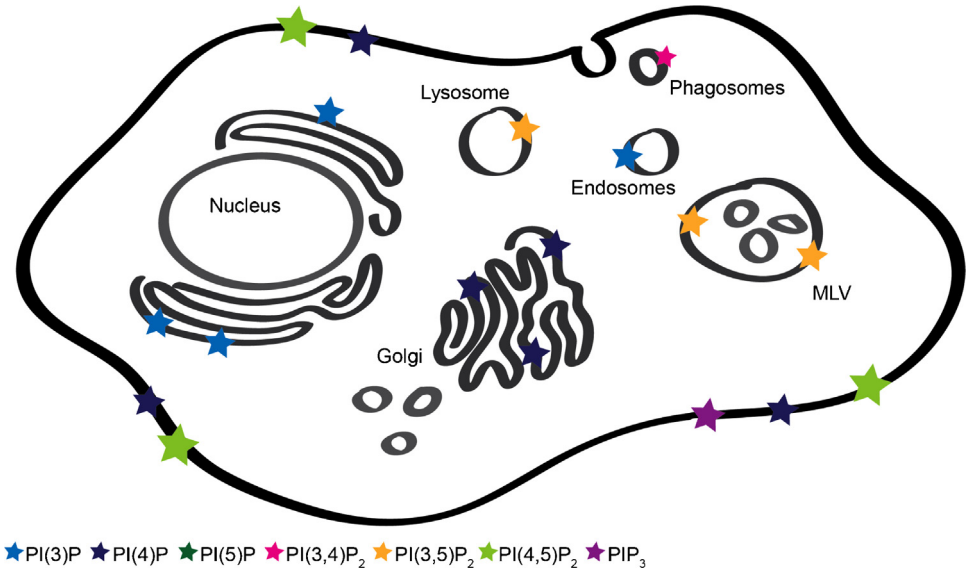

Fig. 1. Cellular distribution of PIPs. A cartoon of a cell is shown to illustrate the known location of PIPs in mammalian cells. The relative abundance of PIPs is depicted with the size of the star shown.

regulate a large number of cellular processes including membrane trafficking, cell growth and survival, cytoskeletal dynamics, and chemotaxis (Di Paolo and De Camilli, 2006; Falke and Ziemba, 2014; Roth, 2004; Balla, 2013). To date the PIP kinases and PIP phosphatases responsible for maintaining the cellular pools of PIPs have been shown to be expressed in the cytosol or at cellular membranes of mammalian cells in a manner that directs the production of distinct pools of PIPs in the cytosolic leaflet of cellular organelles (Balla, 2013) as well as in the nucleus (Balla, 2013; Shisheva, 2013). This distribution enables, at the molecular level, PIPs to selectively regulate membrane trafficking machinery, lipid transfer proteins, enzymes, ion channels, and endocytic and exocytic machinery (Balla, 2013; Di Paolo and De Camilli, 2006).

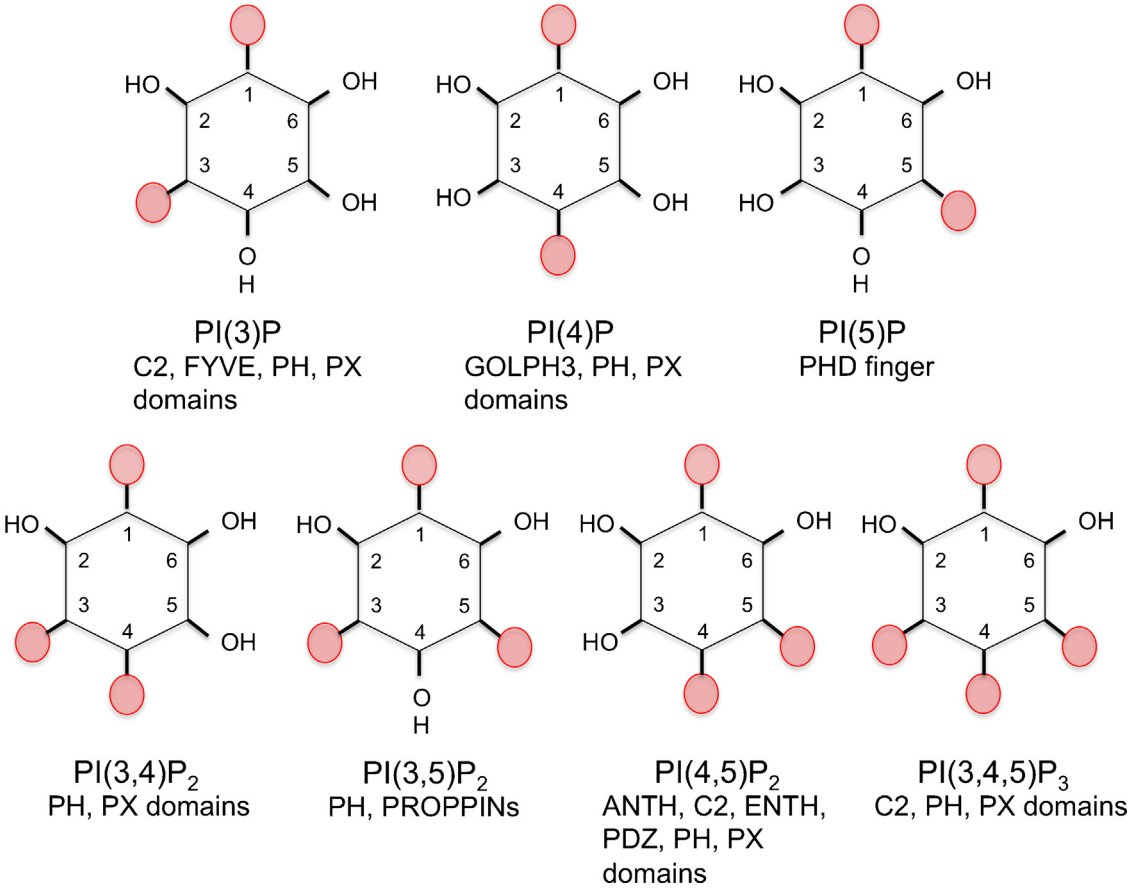

Fig. 2. There are seven different PIPs in mammalian cells that mediate recruitment of peripheral proteins to cellular membranes. The headgroup of each PIP is shown with known effector domains listed below each.