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Review

Mechanistic similarities in docking of the FYVE and PX domains to phosphatidylinositol 3-phosphate containing membranes

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Abstract

Phosphatidylinositol 3-phosphate [PtdIns(3)P], a phospholipid produced by PI 3-kinases in early endosomes and multivesicular bodies, often serves as a marker of endosomal membranes. PtdIns(3)P recruits and activates effector proteins containing the FYVE or PX domain and therefore regulates a variety of biological processes including endo- and exocytosis, membrane trafficking, protein sorting, signal transduction and cytoskeletal rearrangement. Structures and PtdIns(3)P binding modes of several FYVE and PX domains have recently been characterized, unveiling the molecular basis underlying multiple cellular functions of these proteins. Here, structural and functional aspects and current mechanisms of the multivalent membrane anchoring by the FYVE and PX domains are reviewed and compared.

Keywords: FYVE domain; PX domain; Phosphoinositide; Phosphatidylinositol 3-phosphate; Membrane

Contents

Abbreviations: PtdIns(3)P, phosphatidylinositol 3-phosphate; PtdIns, phosphatidylinositol; PI, phosphoinositide; PX, phox homology; MIL, membrane interaction loop; PtdSer, phosphatidylserine; NMR, nuclear magnetic resonance; EGFP, enhanced green fluorescent protein; DPC, dodecylphosphocholine; EEA1, early endosome antigen 1; Hrs, hepatocyte growth factor-regulated tyrosine kinase substrate; SARA, Smad anchor for receptor activation; SNXs, sorting nexins; SNARE, soluble *N*-ethylmaleimide-sensitive fusion protein attachment receptor.

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1. Introduction

Phosphatidylinositol 3-phosphate [PtdIns(3)P] is one of the seven phosphorylated derivatives of PtdIns, a major lipid component of cellular membranes (PtdIns constitutes ~8% of all phospholipids). PtdIns(3)P is produced by PI 3-kinases, which phosphorylate the D3 position of the myo-inositol ring of PtdIns. While only one PI 3-kinase, Vps34p, has been identified in yeast, three different classes of PI 3-kinases (I, II and III) are found in mammals, all with the ability to generate PtdIns(3)P *in vitro* (reviewed in [1–3]). Among them, the mammalian homolog of Vps34p produces the bulk of PtdIns(3)P and appears to specifically phosphorylate PtdIns but not PtdIns(4)P or PtdIns(4,5)P_2. PtdIns(3)P is found primarily in membranes of early endosomes, phagosomes and the internal vesicles of multivesicular bodies in mammalian cells, and in vacuolar and endosomal membranes in yeast. Although PtdIns(3)P is constitutively present at a ~200 μM concentration in human cells [4], its level is modulated by a relatively fast turnover, which occurs largely through internalization into multivesicular bodies and lysosomes (or yeast vacuoles) [5] and by the action of lipid kinases and phosphatases. For example, PtdIns(3)P can be converted into PtdIns(3,4)P_2 and PtdIns(3,5)P_2 by a putative 4-kinase and the 5-kinase PIKfyve [6–9], respectively, or dephosphorylated by the myotubularin family of phosphatases [10]. PtdIns(3)P serves as a reliable marker of endosomes and recruits cytosolic effector proteins involved in regulation of endocytotic machinery and trafficking to the endosomal membranes. A number of such effectors has been identified, the majority of which contain PtdIns(3)P-binding FYVE and PX domains, although C2 domain of Tollip [11] and PH domain of PEPP1 [12] are also able to recognize this PI *in vitro* (Fig. 1). In this review we will focus on the molecular mechanisms of docking of the FYVE and PX domain-containing proteins to PtdIns(3)P-enriched membranes.

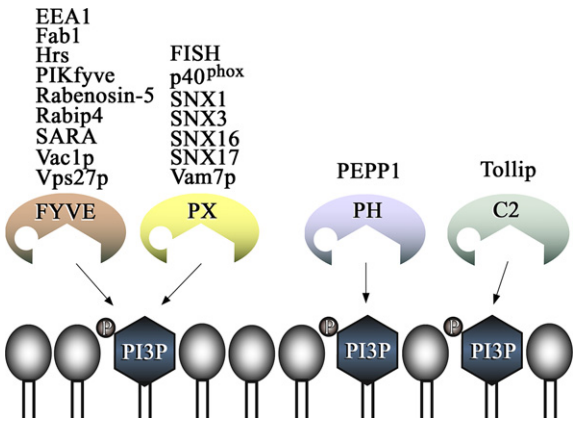

Fig. 1. PtdIns(3)P binding domains. Signaling domains are shown as colored shapes with proteins containing these domains listed above.