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Review

Understanding of the roles of phospholipase D and phosphatidic acid through their binding partners

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ABSTRACT

Phospholipase D (PLD) is a phosphatidyl choline (PC)-hydrolyzing enzyme that generates phosphatidic acid (PA), a lipid second messenger that modulates diverse intracellular signaling. Through interactions with signaling molecules, both PLD and PA can mediate a variety of cellular functions, such as, growth/proliferation, vesicle trafficking, cytoskeleton modulation, development, and morphogenesis. Therefore, systemic approaches for investigating PLD networks including interrelationship between PLD and PA and theirs binding partners, such as proteins and lipids, can enhance fundamental knowledge of roles of PLD and PA in diverse biological processes. In this review, we summarize previously reported protein–protein and protein–lipid interactions of PLD and PA and their binding partners. In addition, we describe the functional roles played by PLD and PA in these interactions, and provide PLD network that summarizes these interactions. The PLD network suggests that PLD and PA could act as a decision maker and/or as a coordinator of signal dynamics. This viewpoint provides a turning point for understanding the roles of PLD–PA as a dynamic signaling hub.

Contents

1. Introduction . . . 72
2. Binding partners of PLD and PA . . . 72
 2.1. The interaction network of PLD and PA . . . 72
 2.2. PLD-binding partners . . . 72
  2.2.1. Phosphoinositides . . . 72
  2.2.2. Small GTPases . . . 72
  2.2.3. Protein kinases . . . 73
  2.2.4. Structural proteins . . . 73
 2.3. PA-binding partners . . . 74
  2.3.1. Kinases and phosphatases . . . 74
  2.3.2. Nucleotide (GTP, ATP, and cAMP) binding proteins . . . 74
  2.3.3. Others . . . 74

Abbreviations: AMPK, AMP-activated protein kinase; ARF, ADP-ribosylation factor; CDK5, cyclin-dependent kinase 5; CEM, caveolin-enriched membrane; CRMP-2, collapsin response mediator protein-2; EGF, epidermal growth factor; EGFR, EGF receptor; GAP, GTPase-activating protein; GDI, guanine nucleotide dissociation inhibitor; GEF, guanine nucleotide exchange factor; GPCR, G protein-coupled receptor; JAK3, Janus kinase 3; LPA, lysophosphatidic acid; mTOR, mammalian target of rapamycin; mTORC1, mTOR Complex 1; PA, phosphatidic acid; PDE, phosphodiesterase; PDGF, platelet-derived growth factor; PH, pleckstrin homology; PI, phosphoinositides; PI(3,4)P2, phosphatidylinositol 3,4-bisphosphate; PI(3,4,5)P3, phosphatidylinositol 3,4,5-trisphosphate; PI(4,5)P_2, phosphatidylinositol 4,5-bisphosphate; PI(5)P, phosphatidylinositol 5-phosphate; PI4P5K, phosphatidylinositol 4-phosphate 5-kinase; PKC, protein kinase C; PKN, protein kinase N; PLD, phospholipase D; PMA, phorbol ester; PP1cγ, the γ isoform of the protein phosphatase-1 catalytic subunit; PX, phox homology; RTK, receptor tyrosine kinase.

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3. Cellular compartments and biological processes . . . 74
3.1. Cellular compartments of binding partners of PLD and PA . . . 75
3.2. Biological processes of binding partners of PLD and PA . . . 75
3.2.1. Vesicle-mediated transport . . . 75
3.2.2. Cytoskeleton organization . . . 76
3.2.3. Survival, growth and proliferation . . . 76
4. Signaling modules of PLD and PA . . . 77
4.1. Positive feedback loops of PLD and PA . . . 77
4.2. Feed-forward loops of PLD, GTPases, and kinases . . . 78
5. Conclusions and perspective . . . 79
Acknowledgements . . . 79
Appendix A. Supplementary data . . . 79
References . . . 79

1. Introduction

Membrane lipid signaling plays key roles in extracellular cell-to-cell communication and intracellular signal transduction via lipid mediators that serve as ligands, second messengers, and docking sites for signaling proteins [1–4]. Phosphatidic acid (PA), a lipid second messenger, is generated by the hydrolysis of phosphatidylcholine (PC) by PLD. PA is considered a key player in the transmission/amplifications of intracellular signals and in the regulation of a variety of cellular functions, such as, cell proliferation, vesicle trafficking, cytoskeletal reorganization, and morphogenesis [5–9]. Therefore, it appears that PLD is an essential regulator that can transmit and amplify intracellular signals by modulating the amount of PA present in diverse signaling contexts. There are two mammalian PLD isoforms, PLD1 and PLD2, which share about 50% amino acid sequence identity [10]. PLD has several conserved regions, such as, the phox homology (PX), pleckstrin homology (PH) and two catalytic regions (the HKD motifs) to generate PA [5]. PLD and PA interact with various types of proteins and lipids to mediate multiple cellular functions [8,9]. However, although the interactions between PLD and PA and several signaling molecules and the potential regulatory roles of PLD and PA via such interactions have been studied, systematic approaches have not been used to determine how PLD and PA collectively regulate signaling cascades at the network level. This review summarizes previously reported protein–protein and protein–lipid interactions of PLD and PA, provides a PLD–PA signaling network based on an integration of all interaction information available for PLD and PA. By analyzing interaction partners at the network level, we then attempted to deduce the roles of PLD and PA. Furthermore, the analysis of network motifs involving PLD and PA in the network suggested that PLD–PA could act as a decision maker and/or a coordinator for orchestrating signaling dynamics as a signaling hub.

2. Binding partners of PLD and PA

Signaling molecules often regulate biological processes by interacting with other signaling molecules. Therefore, overall views of interaction networks are useful for understanding relationships between interacting molecules and their functional roles in signaling networks. In the present study, we first summarized all molecules found to interact with PLD and PA over the past fifteen years.

2.1. The interaction network of PLD and PA

We listed all species reported to interact directly with PLD or PA and then reconstructed an interaction network (Fig. 1A). This network shows that PLD and PA act as signaling hubs that interact with many binding partners. In fact, PLD was found to interact with 58 proteins and 5 lipids, and PA was found to target 50 proteins (Fig. 1B). In addition, several proteins and lipids interact with PLD1 and PLD2 while others interact with PLD1 or PLD2 (Fig. 1B). It should be noted that information regarding interaction specificity is incomplete because some studies checked the presence of interactions with PLD1 and PLD2, whereas others examined interactions with PLD1 or PLD2. See supplementary information for the list of the PLD and PA interactions and detailed information (Tables S1 and S2). The information can also be found at PLD database (http://pld-db.postech.ac.kr).

2.2. PLD-binding partners

The PLD interaction network shows that PLD activity is tightly regulated by multiple interacting factors. Based on their molecular functions, these factors can be categorized as phosphoinositides (PI), small GTPases, protein kinases, structural proteins, and so on (Fig. 1C).

2.2.1. Phosphoinositides

The phosphoinositides are important mediators in the regulation of PLD activity and localization [8]. PLDs have a phosphatidylinositol 4,5-bisphosphate ($PI(4,5)P_2$) binding region [11,12]. The $PI(4,5)P_2$ is a critical lipid cofactor for the regulations of the activities and subcellular localizations of PLDs [8]. Interestingly, phosphatidylinositol 4-phosphate 5-kinase (PI4P5K), which generates $PI(4,5)P_2$, is activated by PLD-produced PA [13,14]. We discuss this feedback loop in detail later in this review. In addition, phosphatidylinositol 3,4,5-trisphosphate ($PI(3,4,5)P_3$) activates PLD1, but to a lesser extent than PIP_2 [15]. Furthermore, $PI(3,4,5)P_3$ has been reported to preferentially bind to the PX domain of PLD1 and promote PLD1 localization to the plasma membrane after stimulation [16,17]. Phosphatidylinositol 5-phosphate (PI(5)P) has also been shown to bind to the PLD1 PX domain and to be required for PLD1 internalization [18]. However, the multiple-relationships between phosphoinositides and PLD in various signaling pathways remain to be elucidated.

2.2.2. Small GTPases

Small GTPases, including ADP-ribosylation factor (ARF) and Rho subfamily, play critical roles in PLD regulation together with the phosphoinositides [8]. ARF was initially identified as an activator of PLD [19,20], and ARF1 activates PLD1 [21,22] and PLD2, although the effect of ARF1 on PLD2 is small [23,24]. ARF6 can also activate both PLDs [25]. However, no direct interaction between ARF6 and PLD2 has been confirmed [26]. The Rho GTPase family, such as RhoA, Rac1, and Cdc42, exclusively activate PLD1 via direct interactions [11,15,27]. Of these Rho family proteins, RhoA is known to be