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Accumulating insights into the role of phospholipase D2 in human diseases

Jaewang Ghim [a], Chaithanya Chelakkot [b], Yoe-Sik Bae [c], Pann-Ghil Suh [d], Sung Ho Ryu [a, *]

[a] Department of Life Sciences, Pohang University of Science and Technology, Pohang, Republic of Korea
[b] Division of Integrative Biosciences and Biotechnology, Pohang University of Science and Technology, Pohang, Republic of Korea
[c] Department of Biological Sciences, Sungkyunkwan University, Suwon, Republic of Korea
[d] School of Life Sciences, Ulsan National Institute of Science and Technology, Ulsan, Republic of Korea

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ABSTRACT

Phospholipase D2 (PLD2) is a lipid-signaling enzyme that produces the signaling molecule phosphatidic acid (PA) by catalyzing the hydrolysis of phosphatidylcholine (PC). The molecular characteristics of PLD2, the mechanisms of regulation of its activity, its functions in the signaling pathway involving PA and binding partners, and its role in cellular physiology have been extensively studied over the past decades. Although several potential roles of PLD2 have been proposed based on the results of molecular and cell-based studies, the pathophysiological functions of PLD2 *in vivo* have not yet been fully investigated at the organismal level. Here, we address accumulated evidences that provide insight into the role of PLD2 in human disease. We summarize recent studies using animal models that provide direct evidence of the function of PLD2 in several pathological conditions such as vascular disease, immunological disease, and neurological disease. In light of the use of recently developed PLD2-specific inhibitors showing potential in alleviating pathological conditions, improving our understanding of the role of PLD2 in human disease would be necessary to target the regulation of PLD2 activity as a therapeutic strategy.

Contents

* Corresponding author.
E-mail address: sungho@postech.ac.kr (S.H. Ryu).

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1. Introduction

Phospholipase D2 (PLD2) is a member of PLD family that catalyzes the hydrolysis of phosphatidylcholine (PC) to yield free choline and phosphatidic acid (PA), a lipid signaling molecule (Jenkins and Frohman, 2005; Tu-Sekine et al., 2015). PLD2 has several domains that are conserved among members of the PLD family (Frohman et al., 1999). PA generation is catalyzed by the HKD domain (HKD, contains the HxKxxxxD motif). The Phox homology (PX) domain and pleckstrin homology (PH) domain are important for interactions with phospholipids and other proteins that facilitate specific PLD2 functions (Exton, 2002; Jang et al., 2012; Lopez et al., 1998; Oude Weernink et al., 2007). Recently, the guanine nucleotide exchange factor (GEF) activity of the PH domain was also reported, expanding the potential areas for PLD2 function (Jeon et al., 2011; Lee et al., 2006).

In several signaling pathways, PLD-generating PA and PLD itself play critical roles in mediating and coordinating signals. Based on the signaling functions, PLD2 activated in response to various stimuli have been known to contribute to a number of cellular functions, such as growth, proliferation, differentiation, migration, vesicle trafficking, and cytoskeleton remodeling (Cazzolli et al., 2006; Lee et al., 2009). The versatile properties of PLD2 have allowed the prediction of possible roles in pathophysiology *in vivo*. However, definitive *in vivo* functions of PLD2 have only recently begun to be demonstrated (Frohman, 2015; Tappia and Dhalla, 2014). Here, we summarize the accumulated direct evidence for the pathophysiological roles of PLD2 from genetically engineered animal models. Future directions for study are also briefly discussed.

2. Pathological functions of PLD2

2.1. Vascular system and diseases

The vascular system is essential for development, maintenance of homeostasis and repair processes by providing paths for oxygen/nutrient supply, and immune cell migration (Carmeliet, 2003, 2005). Blood vessels of the system form a tubular network structure consisting of endothelial cells and other mural cells (Adams and Alitalo, 2007; Coultas et al., 2005). A number of reports have suggested the involvement of PLD2 in signaling pathways mediated by angiogenic factors, such as vascular endothelial growth factor (VEGF), angiopoietin-1 (Ang1), angiotensin II (Ang II), and formyl peptide receptor 2 (FPR2), and in cellular functions of endothelial cells including migration and permeability (Cho et al., 2004; Gorshkova et al., 2008; Jang et al., 2015; Lee et al., 2004; Li et al., 2005; Yoon et al., 2003; Zeiller et al., 2009). Despite its importance, the role of PLD2 in the vascular system has not been extensively studied at an organismal level. The first direct *in vivo* evidence was provided by a study on zebrafish (Zeng et al., 2009). A spatio-temporal expression pattern of the human homologue of PLD in zebrafish provided evidence for the involvement of PLD in early embryonic development. Inhibition of Pld1 by antisense morpholino oligonucleotides led to impaired intersegmental vessel (ISV) development. The results suggest the function of zebrafish Pld1 in vascular development in vertebrates. Our report showed angiogenic functions of PLD2 in a mammalian system using conditional knockout (KO) mice (Ghim et al., 2014). Although no severe defects were detected during either the embryonic or adult stages in endothelial cell-specific KO (eKO) mice or in whole-body KO mice, retinal angiogenesis was delayed at postnatal day 5 in the developmental stage while; however, it was recovered by postnatal day 14. These results implicate PLD2 in contributing to developmental angiogenesis, although the defects can be compensated systemically. Under pathological conditions, however, the angiogenic role of PLD2 became more significant. *Pld2* eKO mice showed decreased pathological angiogenesis during tumor growth and decreased oxygen-induced retinopathy (OIR), in a model for retinopathy of prematurity (ROP) in human. Although pathological angiogenesis shares common processes with physiological angiogenesis, regulatory mechanisms are disrupted during pathological angiogenesis (Chung and Ferrara, 2011). In this study, we suggested that PLD2 requires hypoxia-induced gene expression via the regulation of HIF-1α translation and cellular functions of endothelial cells under pathological conditions.

2.2. Immunological disease

PLD2 is ubiquitously expressed in several cell types, including immune cells. The roles of PLD2 in immune cell functions, such as chemotaxis, phagocytosis, cell spreading, and migration, have been studied at the cellular level (Gomez-Cambronero et al., 2007). The cellular functions of immune cells are largely mediated by cytoskeleton remodeling. PLD2 has been shown to participate in cytoskeleton remodeling by cooperating with other regulatory factors (Colley et al., 1997; Oude Weernink et al., 2007). Thus, PLD2 can modulate the cellular functions of macrophages, lymphocytes, and neutrophils (Ali et al., 2013; Hamdi et al., 2008; Kantonen et al., 2011; Knapek et al., 2010; Lehman et al., 2006; Mahankali et al., 2013; Speranza et al., 2014). However, controversies have arisen over certain functions of PLD2 in immune cells; for example, the contribution of PLD2 to neutrophil physiology through the generation of ROS (Norton et al., 2011; Sato et al., 2013) is debated. Furthermore, the roles of PLD2 in the immune system have not been fully evaluated by *in vivo* studies. Recently, we reported a role for PLD2 in systemic inflammatory response syndrome or sepsis (Lee et al., 2015). *Pld2* KO mice showed increased survival with decreased vital organ damage with experimentally induced sepsis. Increased bactericidal activity and reduced lymphocyte apoptosis and systemic inflammation can explain this protective effect of PLD2 deficiency. In this study, also, neutrophils were identified as key players in PLD2-driven mortality with sepsis. In particular, CXCR2 stabilization on the surface of neutrophils

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