Advances in Biological Regulation xxx (2015) 1–5

Contents lists available at ScienceDirect

Advances in Biological Regulation

journal homepage: www.elsevier.com/locate/jbior

Accumulating insights into the role of phospholipase D2 in human diseases

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ARTICLE INFO

Article history:
Received 4 October 2015
Received in revised form 27 November 2015
Accepted 27 November 2015
Available online xxx

Keywords:
Phospholipase D2
Pathological function
Vascular disease
Immunological disease
Neurological disorder

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.

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http://dx.doi.org/10.1016/j.jbior.2015.11.010
2212-4926/

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

Please cite this article in press as: Ghim, J., et al., Accumulating insights into the role of phospholipase D2 in human diseases, Advances in Biological Regulation (2015), http://dx.doi.org/10.1016/j.jbior.2015.11.010

and upregulated neutrophil extracellular trap (NET) formation elicited recruitment and bacterial killing by neutrophils. These results clearly showed the role of PLD2 in interacting with a specific class of immune cells and in immunological disease.

2.3. Neurological disorder

The expression of PLD2 in tissues of the nervous system is high relative to its expression in other tissues. Many reports have implicated PLD2 in the physiology of neural systems including neurite outgrowth, neurotransmitter release, and astroglial cell proliferation (Burkhardt et al., 2015; Kanaho et al., 2009). The association of PLD activity with neuronal diseases has also been reported (Min do et al., 2007; Peng et al., 2006). Recently, a role for PLD2 in Alzheimer's disease (AD) was suggested by a study using *Pld2* KO mice (Oliveira et al., 2010). Amyloid β-peptide (Aβ), a pathological molecule for AD, enhances PLD activity in cultured neuronal cells. PLD activity is also increased in the brains of transgenic AD mice (SwAPP). Furthermore, PLD2 deficiency can inhibit Aβ-induced suppression of long-term potentiation in hippocampus sections, suggesting critical role for PLD2 in the synaptotoxic effect of Aβ. Finally, PLD2 deficiency rescues cognitive defects observed in SwAPP mice. These results directly support the importance of PLD2 in AD pathogenesis.

2.4. Cancer

PLD2 is considered a critical player in cancer due to its role in cell survival, proliferation, migration, and other key processes. PLD activity and single nucleotide polymorphisms (SNPs) of the *PLD2* gene have been implicated in several types of cancers, such as melanomas, gastric, breast, renal, and colorectal cancers (Park et al., 2012). In colorectal cancer, the tumor size and patient survival correlates with the increased expression of PLD2 (Saito et al., 2007), and point mutations in the *PLD2* gene have been found in breast cancers (Wood et al., 2007). PLD2 and PA coordinate a number of cancer-related signaling pathways, resulting in cell proliferation, invasion, and metastasis (Gomez-Cambronero, 2014). PLD2 modulates cancer cell proliferation by up-regulating mitogenic signaling pathways, including the EGFR-SRC, MAPK, SOS1-RAS, and mTOR pathways (Fang et al., 2001; Joseph et al., 2001; Rizzo et al., 1999; Toschi et al., 2009; Zhao et al., 2007). PLD2 also provides motility signals that lead to cancer cell migration, invasion, and metastasis by modulating cytoskeleton reorganization and membrane ruffling (Honda et al., 1999; Jeon et al., 2011; Shen et al., 2002; Tappia and Dhalla, 2014). Pro-metastatic functions of PLD2 have been shown in lymphoma cells and in a mouse model (Knoepp et al., 2008). In addition to these roles in cancer, PLD also contributes to tumor growth and metastasis in tumor microenvironments (Chen et al., 2012; Ghim et al., 2014). Previous studies strongly support these roles for PLD2 in cancer. Further *in vivo* and clinical studies are required to provide evidence for the effectiveness of PLD modulation in cancer treatment.

3. Conclusions and perspectives

Because of the absence of research tools for *in vivo* evaluation, studies on PLD2 function have been conducted primarily at the molecular and cellular level. Recently, genetically engineered mouse models have been developed, and they have given researchers the opportunity to validate proposed functions and identify novel roles of PLD2 at the organismal level. In contrast to previous expectations, however, PLD2 KO mice have not shown an evident phenotype under normal conditions. Molecular compensation by either other isoform(s) or PA-generating enzymes, or systemic compensation at the organismal level, could be possible explanation for this phenomenon. Much effort has gone into unveiling PLD2 functions in particular conditions such as diseases, allowing better prediction of its functions than normal conditions. Recent reports have suggested specific contributions of PLD2 to pathological conditions, such as pathological angiogenesis, sepsis, and Alzheimer's disease. However, many pathophysiological conditions, including cancer development, remain to be tested. In addition, because PLD2 is expressed ubiquitously in most cell types, more intricate studies using conditional KO (tissue-specific and inducible) animal models are required to clearly reveal the cell-, tissue-, and organ-specific functions of PLD2. Recent studies have shown ameliorating effects of isotype-specific inhibitors of PLD on some diseases. The new inhibitors overcame limitations of previously used pan-PLD inhibitors. Furthermore, the use of an effective PLD2 inhibitor will provide opportunities to better understand PLD2 functions in various disease conditions and suggest potential therapeutic strategy for these diseases.

Acknowledgments

This work was supported by grant No: NRF-2015R1A2A1A13001834 of the National Research Foundation, funded by the Ministry of Education, Science and Technology of Korea.

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Please cite this article in press as: Ghim, J., et al., Accumulating insights into the role of phospholipase D2 in human diseases, Advances in Biological Regulation (2015), http://dx.doi.org/10.1016/j.jbior.2015.11.010

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