Molecules and Cells

Minireview

Phospholipase D and Its Essential Role in Cancer

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The role of phospholipase D (PLD) in cancer development and management has been a major area of interest for researchers. The purpose of this mini-review is to explore PLD and its distinct role during chemotherapy including anti-apoptotic function. PLD is an enzyme that belongs to the phospholipase super family and is found in a broad range of organisms such as viruses, yeast, bacteria, animals, and plants. The function and activity of PLD are widely dependent on and regulated by neurotransmitters, hormones, small monomeric GTPases, and lipids. A growing body of research has shown that PLD activity is significantly increased in cancer tissues and cells, indicating that it plays a critical role in signal transduction, cell proliferation, and anti-apoptotic processes. In addition, recent studies show that PLD is a downstream transcriptional target of proteins that contribute to inflammation and carcinogenesis such as Sp1, NFκB, TCF4, ATF-2, NFATc2, and EWS-Fli. Thus, compounds that inhibit expression or activity of PLD in cells can be potentially useful in reducing inflammation and sensitizing resistant cancers during chemotherapy.

Keywords: anti-cancer drug, apoptosis, cancer, inhibitor, PLD

INTRODUCTION

Cancer is one of the leading causes of death and poor health around the world (Kushi et al., 2012; Weir et al., 2016). Healthy cells grow and die in a controlled manner. However, those who suffer from cancer experience uncontrolled cell growth (DeVita, 2002; Pedraza-Farina, 2006). Over the years, attempts have been made to develop interventions that can be used to manage cancer and reverse its adverse health outcomes (Cunningham et al., 2010; Mantovani, 2010; Samaras et al., 2010). One of the widely used interventions in cancer management and control is chemotherapy. According to Weaver, chemotherapy can decrease growth and proliferation, limit metastasis, and promote death in cancer cells (Weaver, 2014). However, most treatment can also harm healthy cells and cause undesirable side effects (Fabbrocini et al., 2012; MacDonald, 2009; Wettergren et al., 2012).

The use of chemotherapy in treating cancer started in the 20th century (DeVita and Chu, 2008). The main goal in administering chemotherapy is to reduce the burden of the disease and help patients live a healthy and fulfilling life (Chabner and Roberts, 2005; Chen et al., 2007; Fabbrocini et al., 2012). However, a long list of serious, adverse side effects— including pain, hair loss, vomiting, nausea, and fatigue— have limited its application (Chabner and Roberts, 2005; Chen et al., 2007; Fabbrocini et al., 2012). Because these side effects are undesirable and detrimental to the well-being of patients, researchers and healthcare practitioners are constantly searching for new interventions and drugs that have the potential to improve effectiveness against cancerous tissue and/or alleviate adverse effects on healthy tissue (DeVita and Chu, 2008). Phospholipase D (PLD) is potential target of new drugs that can increase chemotherapeutic efficacy and decrease toxicity and side effects caused by chemotherapy. In particular, the inhibition of PLD during treatment can sensitize cancer cells to chemotherapy. The

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purpose of this paper is to review PLD and its anti-apoptotic role during chemotherapy.

PHOSPHOLIPASE D

PLD is an enzyme that belongs to the phospholipase superfamily. Phospholipases occur widely and are found in a broad range of organisms such as viruses, yeast, bacteria, animals, and plants (Frohman, 2015; Nelson and Frohman, 2015; Zhang and Frohman, 2014). The primary substrate in PLD is phosphatidylcholine (PC) which is one of the most abundant components found in the lipid bilayer of the plasma membrane. As shown in Fig. 1A, PC is composed of a choline head, a phosphate, a glycerol and two fatty acids. PC can be quickly hydrolyzed by PLD to generate soluble choline and a signaling molecule known as phosphatidic acid (PA) (Billah et al., 1989). Previous studies have shown that mammalian cells encode two PLD isoforms; PLD1 and PLD2 (Colley et al., 1997; Nakashima et al., 1997). Since this discovery, PLDs have been studied intensively and it has been noted that these two isoforms play a vital role in physiological processes in the body, including receptor-mediated endocytosis, cell migration, and cytoskeletal reorganization (Colley et al., 1997; Kang et al., 2014). Furthermore, they have been implicated in the pathophysiology of various diseases such as the progression of cancer, Alzheimer's disease, and Parkinson's disease (Bae et al., 2014; Jin et al., 2006).

The actual function of PLD and its influence on cellular processes have been an important area of focus and interest for researchers. PLD is a form of transphosphatidylase that mediates and influences the exchange of polar head groups, which are covalently bonded to various membrane-bound lipids. The process entails using water as the nucleophile to catalyze phosphodiester bonds found in different phospholipids such as phosphatidylethanolamine and PC.

As shown in Fig. 1B, PLD can hydrolyze PC into choline and lipid PA, as well as catalyze transphosphatidylation in the presence of primary alcohols where the phosphatidyl group is transferred to the alcohol to generate phosphatidyl alcohol (Yang et al., 1967). In this mechanism transphosphatidylation refers to the process of head group exchange among glycerophospholipids achieved when PLD acts on the phospholipid polar head as phosphodiesterase (Brown et al., 2007; Walker and Brown, 2004). It is imperative to note that in this reaction, the acceptor alcohol competes with the water molecule for the phosphatidyl moiety. Lerchner et al. (2005) assert that the transphosphatidylation potential of PLDs from different sources depends on the chemical and spatial surrounding of the two HKD motifs. HKD motifs are the catalytic domains of PLD containing a distinct sequence (HxxxxxxxKxD) where H (histidine), K (lysine), and D (aspartic acid) are highly conserved amino acids vital to its function. Generally, primary alcohols are better acceptors than secondary alcohols. Available research evidence further shows that the catalytic potential of PLD is not restricted to the phosphatidyl backbone but also allows modifications in the nonpolar residue (Selvy et al., 2011).

The function and activity of PLD are widely dependent on and regulated by neurotransmitters, hormones, small monomeric GTPases, and lipids. In most instances, the signal transduction is typically mediated through the generation of PA. Several studies have identified specific phospholipids that act as regulators of PLD function and activity in both animal and plant cells (Selvy et al., 2011). In most of these studies, researchers have indicated that PLD requires phosphatidylinositol 4, 5-bisphosphate (PIP_2) as one of the primary cofactor

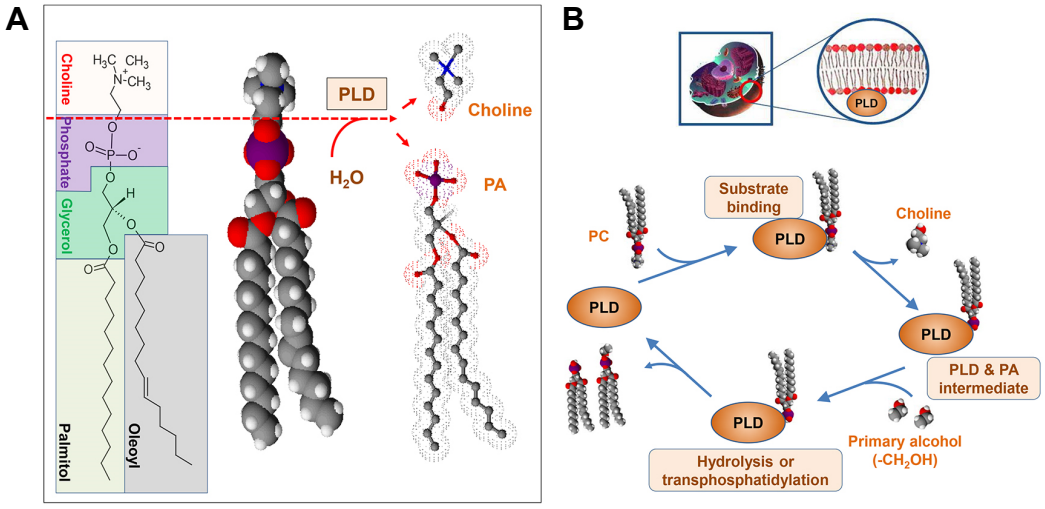


Fig. 1. Structure of a PC and enzymatic reaction of PLD with PC, hydrolysis or transphosphatidylation. (A) Phosphatidylcholine, a lipid formed from a choline head, a phosphate, a glycerol and two fatty acids. (Dark gray: carbon atoms; Light gray: hydrogen atoms; Red: oxygen atoms; Violet: phosphorus atom; Blue: nitrogen atom.). (B) The model summarizes of catalytic mechanism of PLD in biochemical reaction. Catalysis proceeds via the formation of PA (a covalent enzyme) intermediate. Hydrolysis or transphosphatidylation involves nucleophillic attack on the diester phosphate group of this intermediate by water or the hydroxyl group of a primary alcohol. PA, phosphatidic acid; PC, phosphatidylcholine; PLD, phospholipase D.

for its function and activity (Oude Weernink et al., 2007; Preininger et al., 2006). PIP_2 and other cofactors such as phosphoinositides have been identified as important modifiers that influence the ability of PLD to carry out its functions, including intracellular signal transduction. It is important to note that most cell types of human exhibit activities of both major mammalian PLD isoforms, PLD1 and PLD2, excluding peripheral leukocytes and other groups of lymphocytes (Colley et al., 1997; Hammond et al., 1995).

PLD1 (120 kDa) is an enzyme mainly found in the inner membranes of mammalian cells including the secretory granules, endosomes, lysosomes, and Golgi complex (Colley et al., 1997; Corrotte et al., 2006; Nanjundan and Possmayer, 2003). When the protein binds with an extracellular stimulus, it is readily transported to the plasma membrane (Choi et al., 2002). PLD1 exhibits low intrinsic activity, and is unable to transduce an extracellular signal at its basal level. It must therefore be activated by various proteins such as protein kinase C (PKC), Rac, Rho, and Arf to allow extracellular transduction. The process is usually stimulated by a wide range of agonists that act through receptor tyrosine kinases (RTKs) and G protein-coupled receptors (GPCRs). The PC-specific PLD1 activity and function have been implicated in various cellular pathways such as membrane trafficking, mitosis regulation, and signal transduction (Cho et al., 2008; Hammond et al., 1995; Lee et al., 2001).

The second PLD isoform, PLD2 (106 kDa) is usually localized to the plasma membrane and has been linked to high catalytic activity. The available evidence shows that PLD2 displays the same enzymatic activity as PLD1, catalyzing the hydrolysis of PC to produce choline and PA. It is also worth noting that the hydrolysis process is usually activated and stimulated by GPCRs and RTKs (Lopez et al., 1998; Zhao et al., 2007). Colley et al. posit that the PLD2-specific hydrolysis of PC influences some cellular processes such as cytoskeletal reorganization, regulated secretion, and cell cycle control (Colley et al., 1997).

PLD SIGNALING PATHWAYS

Previous studies have exhaustively reviewed the mechanisms surrounding PLD signaling pathways (Foster et al., 2014; Jang et al., 2012; Park et al., 2012). PLD can be activated by a wide range of extracellular signals that include growth hormones, insulin, epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), sphingosine 1-phosphate (S1P), and lysophosphatidic acid (LPA) (Alberghina, 2010; Cho et al., 2004; Oude Weernink et al., 2007; Suh et al., 2008). The extracellular signals usually stimulate PLD through the direct activation of GPCRs or the RTKs (Lee et al., 2009). PLD can also transmit signals to various downstream molecules through lipid mediators. In such cases, the PLD and its lipid mediators usually induce a hierarchical and multi-layered signaling network (Aoki et al., 2007; Lee et al., 2009). In addition, lipid mediators play a fundamental role in the participation of a broad range of cellular processes related to metastasis and tumorigenesis such as actin cytoskeleton reorganization, proliferation, angiogenesis, inflammation, growth, and matrix metallo-proteinase (MMP) secretion (Murakami et al., 2011; Suh et al., 2008; Wang et al., 2006).

PA, the main messenger generated by both PLD1 and PLD2, functions pleiotropically (Cruchaga et al., 2014; Liscovitch et al., 1993; Osisami et al., 2012). According to Ammar et al. (2013) PA possesses a small negatively charged head group that can drive membranes to undergo significant negative curvature where there is sufficient concentration of PA. The negative curvature ends to lower energy activation during the production of membrane vesicles and their subsequent fusion into the target membranes. In the process, it facilitates membrane vesicle trafficking, and endocytosis / exocytosis (Ammar et al., 2013). PA can also act as a lipid anchor, functioning to recruit PA-binding proteins to localized sites of signal transduction (Nishikimi et al., 2009; Zhao et al., 2007). In some cases, PA can activate proteins such as phosphatidylinositol 4-phosphate 5-Kinase (PI4P5K) and mTOR to regulate cellular processes such as cell hypertrophy, survival, and differentiation. Finally, PA can be dephosphorylated by Lipin to produce diacylglycerol (DAG) or hydrolyzed by phospholipase A (PLA) to produce LysoPA (Aoki, 2004; Baba et al., 2014). DAG and LysoPA are potent and important signaling lipids that can also be converted into PA by the DAG kinases (DGKs) and LysoPA acetyltransferases (LPAATs) respectively (Csaki et al., 2013; Foster et al., 2014).

The significance of PLD, its products and cues of its signaling pathways such as the lipid mediators in critical cellular functions have been highlighted in cell based assays as well as in analysis of knockout and transgenic mice (Murakami et al., 2011; Park et al., 2012; Suh et al., 2008). Some studies have used knockout mice to show that the PLD signaling pathway may have important role in cognitive dysfunctions observed in fetal alcohol syndrome and Alzheimer's disease (Burkhardt et al., 2014). In addition distinct tumor-related phenotypes such as metastasis, tumorigenesis and angiogenesis can be shown in PLD1 knock-out mouse model (Chen et al., 2012).

THE ROLE OF PLD AND ITS ANTI-APOPTOTIC EFFECT IN CANCER

The role of PLD in the development of diseases such as cancer and thrombotic diseases has been an area of focus for researchers. In particular, cellular studies have examined how cancer influences PLD expression (Chen et al., 2012; Elvers et al., 2010; Schonberger et al., 2014; Stegner et al., 2013). Bruntz et al. posits that PLD1 activity and expression are usually increased in various types of cancers (Bruntz et al., 2014a). However, the significance of this particular observation remains uncertain due to the fact that PLD1's chromosomal position at 3q26 is adjacent to the position of PI3Kinase-α, which is strongly amplified in various types of cancers (Dhingra et al., 2010; Gobel et al., 2014). Other studies have reported that the PLD signaling mechanism and pathways tend to be complex (Bruntz et al., 2014b; Han et al., 2014; Park et al., 2009). The process includes the upregulation of HIF1-α, activation of AKT, and increased MMP-2 and VEGF secretion.

Variations in PLD2 levels have been observed as well in different types of cancers such as gastric, breast, kidney, and colorectal cancers (Henkels et al., 2013; Toschi et al., 2008; Yamada et al., 2003). In particular, recent studies have shown that transfection of a miR-203 mimic into human glioma cells can directly downregulate PLD2 expression (Chen et al., 2014). In other cases, researchers have observed that the overexpression of PLD2 can rescue the effects induced by miR-203 mimic (Fite et al., 2016). The miR-203 is a noncoding RNA molecule that can regulate the expression of other genes through various mechanisms such as argonaute-based messenger RNA cleavage and translational repression (Bartel, 2009). In human breast cancer studies, researchers have linked increased expression of PLD2 in tumor cells to the suppression of apoptosis and also to the increased tumor growth rate and chemoresistance (Henkels et al., 2013). A number of stimuli including growth factors and oncogenic activation which enhance PLD activity are able to induce hypoxia-inducible factor-1α (Hif-1α) protein which is a heterodimeric transcription factor composed of the basic helix-loop-helix-PAS domain and play an important role in tumorigenesis. Ghim et al. stated that the ablation of PLD2 from the endothelial cells leads the suppression of hypoxia-induced Hif-1α expression, VEGF secretion, and reduced proximal tumor neovascularization (Ghim et al., 2014). While the overall PLD2 expression can vary from one tumor type to another, the available body of research suggests not only a positive correlation between tumor size and PLD2 expression level, but also a negative correlation between PLD2 expression and survival rate in patients suffering from cancers such as colorectal carcinoma (Saito et al., 2007). A more recent study comparing immunohistochemical staining of 30 different human colon cancer samples showed that there was a high level of correlation between PLD2 and Hif-1α (Liu et al., 2015). Also, the study revealed that PLD2 and Hif-1α expression levels were higher in colon cancer tissues in comparison to normal colon issues. Finally, the researchers found out that under hypoxic conditions, PLD2 expression in colon cancer cells was upregulated by Hif1-α (Liu et al., 2015). Thus, PLD2, just like PLD1, appears to be a significant therapeutic target in the treatment and management of different forms of cancers.

In the context of cancer development and management, the anti-apoptotic effects of PLD have attracted the attention of researchers (Le Stunff et al., 2002; Lee et al., 2004). PLD is also known to act as a significant and potent virulence factor and an anti-apoptotic agent. In particular, the substance can inhibit the spontaneous as well as the Fas-stimulated apoptosis in neutrophils. A study reported that the anti-apoptotic effect of PLD involved both the generation of lysoPA from lysophosphatidylcholines and the mobilization of Ca^{2+} through the pertussis-toxin-sensitive G-protein (Lee et al., 2004). Several studies have shown that inhibition of apoptosis can occur in various sites. First, PLD blocks the overexpression of Fas-associated protein with death domain (FADD) and facilitates the degradation of procaspase-8 (Lim et al., 2002). Secondly, PLD tends to block Fas-stimulated Mcl-1 degradation and stabilizes mitochondrial membrane (Lee et al., 2004).

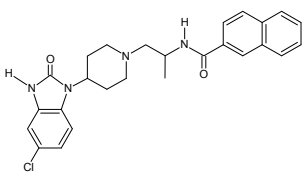
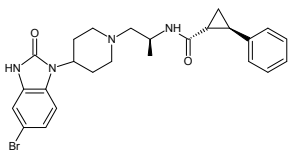
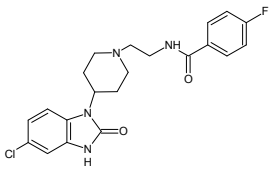
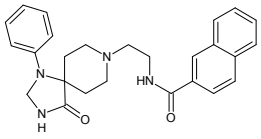
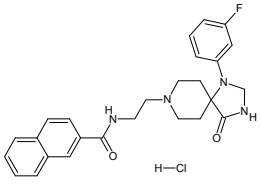
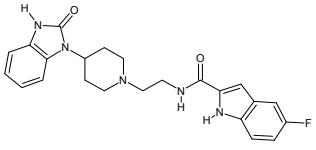
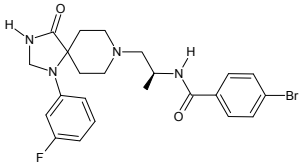
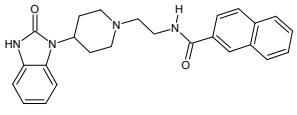
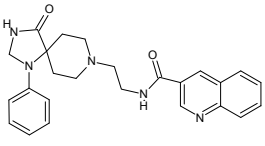
A growing body of research evidence indicates that PLD activity is increased significantly in cancer tissues and cells, showing that it may play a critical role such as signal transduction, cell proliferation, and anti-apoptotic processes (Choi et al., 2009; Joseph et al., 2002; Min et al., 2001; Pyne and Pyne, 2000; Takuwa et al., 2001). Also, studies have shown that PLD plays a key role in sphingosine 1-phosphate (S1P)-receptor-mediated phosphoinositide 3-kinase (PI3K) and Akt activation. In addition, it influences the activation of S1P and insulin growth factor 1 (IGF-1)-induced extracellular-signal-regulated kinase (ERK). S1P affects cellular survival and growth by decreasing serum and ceramide withdrawal-induced apoptosis in cancer tissues and cells. These findings suggest that PLD is widely implicated in anti-apoptosis and survival (Dhingra et al., 2010; Jang et al., 2008; Zhao and Natarajan, 2009). In addition, they demonstrate that the molecular mechanism and pathway which PLD responds to apoptotic stimuli still remain to be further elucidated.

INHIBITOR DEVELOPMENT AND DOWN-REGULATING PLD EXPRESSION

Several compounds are known to suppress the proliferation of cancer cells via down regulation of PLD (Dent et al., 2004; Farooqui and Horrocks, 2005). Available evidence shows that PLD is a downstream transcriptional target molecule of Sp1, NFκB, TCF4, ATF-2, NFATc2, and EWS-Fli, all of which contribute to inflammation and carcinogenesis (Brown et al., 2007; Gomez-Cambronero, 2010; Gozgit et al., 2007; Pannequin et al., 2007). Therefore, compounds that suppress or inhibit these transcription factors can regulate PLD expression with the possible result of reducing inflammation and sensitizing resistant cancers during chemotherapy (Choi et al., 2004; Stringer et al., 2007; Sultani et al., 2012). There are several candidate compounds with the potential to inhibit PLD activity. For instance, triptolide has been used as a Chinese traditional medicine to protect against cancer cell proliferation and inflammation. Rebamipide suppresses both the activity and expression of PLD1and PLD2 in various cancer cells leading to the inhibition of proliferation (Brown et al., 2007; Pannequin et al., 2007). Fodrin, synaptojanin, and amphiphysins are the other molecules that have been shown to control PLD1 and PLD2 activity indirectly (Su et al., 2009). In our study to explore the inhibitory pathway of PLD, human AP180 (hAP180) showed a PLD1 specific inhibitory effect in human stomach cancer cells, SNU484. According to the results, the hAP180 inhibited phobol-12-myristate 13-acetate (PMA)-induced PLD activity resulted in the exacerbation of anti-cancer drug-induced cell death. More specifically, amino acids from Thr312 to Pro314 in hAP180 were critical in the regulation of PLD1 activity and provided potential target of PLD1 inhibitor development (Cho et al., 2011).

In addition, there are several PLD1 and PLD2 specific inhibitors that are available in the market (Table 2). The specific PLD1 inhibitors, VU0155069 and VU-0359595 (Scott et al., 2009), suppress both the activity and expression of PLD1 in various cancer cells leading to the inhibition of proliferation (Brown et al., 2007; Pannequin et al., 2007). Halopemide, NOPT, VU-0364739 are common PLD2 specific inhibitors

Table 1. List of PLD inhibitors and their specific target(s).

Target	Name (Chemical formula)	Full name	Synonym	Structure	References
PLD1	VU-0155069 ($C_{26}H_{27}ClN_4O_2$)	N-[2-[4-(5-chloro-2,3-dihydro-2-oxo-1H-benzimidazol-1-yl)-1-piperidinyl]-1-methylethyl]-2-naphthalenecarboxamide	CAY10593		(Scott et al., 2009)
	VU-0359595 ($C_{25}H_{29}BrN_4O_2$) (1,700-fold selective vs PLD2)	(1R,2R)-N-((S)-1-(4-(5-Bromo-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidin-1-yl)propan-2-yl)-2-phenylcyclopropanecarboxamide	CID-53361951, ML-270		(Lewis et al., 2009)
PLD2	Halopemide ($C_{21}H_{22}ClFN_4O_2$)	N-[2-[4-(5-chloro-2,3-dihydro-2-oxo-1H-benzimidazol-1-yl)-1-piperidinyl]-ethyl]-4-fluoro-benzamide	NSC 354856, R34301		(Scott et al., 2009)
	NOPT ($C_{26}H_{28}N_4O_2$)	N-[2-(4-oxo-1-phenyl-1,3,8-triazaspiro[4,5]dec-8-yl)ethyl]-2-naphthalene-carboxamide	VU0155072-2, CAY10594		(Lavieri et al., 2010)
	VU-0364739 ($C_{26}H_{27}FN_4O_2 \cdot HCl$)	N-[2-[1-(3-Fluorophenyl)-4-oxo-1,3,8-triazaspiro[4.5]dec-8-yl]ethyl]-2-naphthalenecarboxamide hydrochloride	-		(Lavieri et al., 2010)
PLD1/2	Fifi ($C_{23}H_{24}FN_5O_2$)	5-fluoro-2-indolyldes-chlorohalopemide	-		(Monovich et al., 2007)
	ML-299 ($C_{23}H_{26}BrFN_4O_2$)	4-bromo-N-[(1S)-2-[1-(3-fluorophenyl)-4-oxo-1,3,8-triazaspiro[4.5]dec-8-yl]-1-methylethyl]-benzamide	CID-56593087		(Scott et al., 2010)
	VU-0155056 ($C_{25}H_{27}N_5O_2$)	N-(2-{4-[2-oxo-2,3-dihydro-1H-benzo(d)imidazol-1-yl]piperidin-1-yl}ethyl)-2-naphthamide	-		(Scott et al., 2009)
	VU-0285655-1 ($C_{25}H_{27}N_5O_2$)	N-{2-[4-oxo-1-phenyl-1,3,8-triazaspiro(4.5)decan-8-yl]ethyl}quinoline-3-carboxamide	APV		(Lavieri et al., 2009)

(Lavieri et al., 2010; Su et al., 2009). These substances suppress PLD2 activity through various pathways such as blocking phosphatidic acid production and biological processes that are mediated by PLD expression (Su et al., 2009). There are certain inhibitors that are known to affect the activity of both PLD1 and PLD2, including Fifi, ML-299, VU-0155056, and VU-0285655-1 (Lavieri et al., 2009; Scott et al., 2009). Table 1 below gives some of the available inhibitors for PLD1 and/or PLD2. The compounds mentioned above and those listed in Table 1 are known to directly or indirectly inhibit the activity of PLD1 and/or PLD2. However, the clinical utility of the substances when it comes to managing cancer seems to be limited due to inadequate evidence on their specific signaling pathways. Despite this being the cases, studies such as Scott et al. have strived to identify specific inhibitors and examine their signaling pathways with the goal of providing new evidence that can be used to develop therapeutic drugs for managing and treating cancer (Scott et al., 2009).

CONCLUSIONS

A review of previous studies shows that PLDs are essential and important mediators of intracellular and intercellular processes and signaling. These proteins can function as phospholipid-hydrolyzing enzymes and generate bioactive mediators, such as PA, to regulate and influence cellular processes such as tumorigenesis, migration, proliferation, angiogenesis, and invasion. While PLD has been extensively studied, there is a poor understanding of the molecular mechanisms differentially regulating PLD isozyme expression and the precise role of each isoform. In addition, it is unclear whether PLD isozyme is regulated in a coordinated fashion or separately in cancer and inflammation. Despite this, the study of PLD is promising in the field of anti-cancer drug discovery.

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