Role of Ca^{2+}-independent phospholipase A$_2$ in cell growth and signaling

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Abstract

Phospholipase A$_2$(PLA$_2$) are esterases that cleave glycerophospholipids to release fatty acids and lysophospholipids. Several studies demonstrate that PLA$_2$ regulate growth and signaling in several cell types. However, few of these studies have focused on Ca^{2+}-independent phospholipase A$_2$(iPLA$_2$ or Group VI PLA$_2$). This class of PLA$_2$ was originally suggested to mediate phospholipid remodeling in several cell types including macrophages. As such, it was labeled as a housekeeping protein and thought not to play as significant of roles in cell growth as its older counterparts cytosolic PLA$_2$(cPLA$_2$ or Group IV PLA$_2$) and secretory PLA$_2$(sPLA$_2$ or Groups I–III, V and IX–XIV PLA$_2$). However, several recent studies demonstrate that iPLA$_2$ mediate cell growth, and do so by participating in signal transduction pathways that include epidermal growth factor receptors (EGFR), mitogen activated protein kinases (MAPK), mdm2, and even the tumor suppressor protein p53 and the cell cycle regulator p21. The exact mechanism by which iPLA$_2$ mediates these pathways are not known, but likely involve the generation of lipid signals such as arachidonic acid, lysophosphatidic acid (LPA) and lysophosphocholines (LPC). This review discusses the role of iPLA$_2$ in cell growth with special emphasis placed on their role in cell signaling. The putative lipid signals involved are also discussed.

Keywords

Phospholipase A$_2$; Ca^{2+}-independent phospholipase A$_2$; Cell growth; Cell signaling; Arachidonic acid; Lysophosphatidic acid

1. Introduction

Phospholipase A$_2$(PLA$_2$) are esterases that cleave glycerophospholipids at the *sn*-2 ester bond, releasing a fatty acid and a lysophospholipid [1]. They are broadly defined into five different types; secretory PLA$_2$(sPLA$_2$), cytosolic PLA$_2$(cPLA$_2$), Ca^{2+}-independent PLA$_2$(iPLA$_2$), platelet-activating factor hydrolases (PAF-AH) and lysosomal PLA$_2$[2-4]. sPLA$_2$ are the oldest class of PLA$_2$, typically the smallest (13-18 kDa) and use histidine to hydrolyze the *sn*-2 ester bond [3]. In contrast, cPLA$_2$ and iPLA$_2$ are larger in size, typically

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66–90 kDa, and use a serine to catalyze the hydrolysis of the *sn*-2 ester bond [3]. PAF-AH hydrolyze acetyl groups from PAF using a catalytic serine, range in size from 26 to 45 kDa, and include lipoprotein-associated PLA_2[4]. Lysosomal PLA_2 are among the newest class of PLA_2 to be identified. Only one group member is known to exist, which is 45 kDa in size and utilizes a catalytic serine to hydrolyze the *sn*-2 bond at the C-1 position of ceramide [4]. As its name implies, lysosomal PLA_2 localizes to lysosomes [4].

A newer classification system organizes PLA_2 based on their genetic sequence into 15 groups (designated by a roman numeral), encompassing over 20 individual members (designated by Arabic letters) [4]. Several recent reviews discuss PLA_2 as a group, including those dealing with their classification, function and roles in the brain, heart and cancer cells [1,5,6]. Some even discuss roles of PLA_2, in general, on cell growth and death [2,7]. This review focuses on the specific role of $iPLA_2$ in cell growth and signaling.

Several studies, and some reviews, have previously suggested roles for $iPLA_2$ in cell regulation, growth and death [6-8]. Some have even suggested roles for $iPLA_2$ in cell signaling [7,8]. However, several recent studies, all published within the last 2 years, suggest novel roles for $iPLA_2$ in signal transduction pathways that include EGFR, MAPK, the tumor suppressor protein p53 and the cell cycle regulator p21 [9-13]. These new studies suggest that $iPLA_2$ play more significant roles in cell growth than previous thought, and suggest that $iPLA_2$ may be therapeutic targets for alteration of a number of pathologies including cancer, heart disease, renal failure and atherosclerosis.

2. Classification and function of $iPLA_2$

2.1. Types of $iPLA_2$

$iPLA_2$ are referred to as Group VI PLA_2 using the newer classification system and there are at least six known members [4,14] (Table 1). Group VIA-1 and A-2 are splice variants of the same gene and are expressed in the cytosol [15]. Group VIA-1 is commonly referred to as $iPLA_2$ while A-2 is commonly called $iPLA_2\beta$. Group VIB is a distinct gene product localized to the endoplasmic, peroxisomal, and mitochondrial membranes [16,17] and is usually called $iPLA_2\gamma$.

The most recent $iPLA_2$ to be discovered are Group VIC-F and are referred to as $iPLA_2\delta$, $iPLA_2\varepsilon$, $iPLA_2\zeta$ and $iPLA_2\eta$, respectively [4,18,19]. For the purposes of this review we will now refer to $iPLA_2$ using their properly designated group numbering system [4] (Table 1). Differences in the function of each of these enzymes have recently been reviewed [4], and will not be re-covered here. However, a discussion of general functions of Group VI PLA_2 is warranted.

2.2. General functions of Group VI PLA_2

A majority of what we know about the function of Group VI PLA_2 comes from studies in macrophages and mostly applies to Groups VIA and VIB PLA_2. These studies suggest that these enzymes are involved in the maintenance of membrane phospholipids under normal conditions [2,20,21]. This includes the generation of lysophospholipid acceptors that are re-incorporated with fatty acids. This is one way by which Group VI PLA_2 regulate fatty acyl

turnover. Group VI PLA$_2$ also produce arachidonic acid and lysophospholipids in several cell lines [14,21-24], and recent studies suggest roles for Group VI PLA$_2$ in the generation of LPA [25,26].

The ability of Group VI PLA$_2$ to generate lysophospholipid acceptors and regulate fatty acyl-turnover resulted in them being labeled as "housekeeping" proteins. As a result it was originally thought that they did not play as prominent of roles in the generation of arachidonic acid as Group IV PLA$_2$ or Groups I-III, V and IX-XIV PLA$_2$(sPLA$_2$) [6,27-32]. The reality of this situation is that Group VI PLA$_2$ do play "housekeeping" roles by facilitating phospholipid remodeling and maintaining phosphatidylcholines [21,33-36]. Group VI PLA$_2$ complete these tasks while releasing relatively low level of arachidonic acid or LPA, which limits inflammation and cell death.

It should be noted that Group VI PLA$_2$ roles as housekeeping enzymes might not apply to all cells. In fact, studies in INS-1 cells suggest that Group VI PLA$_2$ may play more significant roles in cell signaling than phospholipid remodeling [33,35,37]. Thus, the functions of Group VI PLA$_2$ appear cell dependent.

2.3. Methods for inhibition of Group VI PLA$_2$

Much of what we know about the function of Group VI PLA$_2$ in cell physiology is derived from studies using pharmacological and molecular inhibitors. The pharmacological inhibitor of choice for Group VI PLA$_2$ is bromoenol lactone (BEL or (E)-6-(1-bromoethyl) tetrahydro-3-(1-naphthalenyl)-2H-pyran-2-one)). Other inhibitors include methyl arachidonyl flourophosphonate (MAFP) and arachidonyl triflouromethylketone (AAOCF$_3$). These inhibitors are available from a variety of sources including Cayman Chemical Company (Ann Arbor, MI) and Sigma (St. Louis, MO). The selectivity and specificity of these agents for Group VI PLA$_2$ have been recently, and thoroughly, reviewed [1,4], and will not be covered in detail here. However, it is important to note that MAFP and AAOCF$_3$ both inhibit Group IV PLA$_2$(cPLA$_2$) at concentrations around 5–10 μM [1,38] (Table 1).

BEL selectively inhibits Group VI PLA$_2$ in several cell models at concentrations around 2–5 μM [1,39]. BEL also inhibits phosphatidate phosphohydrolase (PAP-1) [36]. However, PAP-1 is inhibited by propranolol, which does not inhibit Group VI PLA$_2$. Using a combination of MAFP, AAOCF$_3$, BEL and propranolol will allow one to distinguish between events mediated by Group IV and VI PLA$_2$, and eliminate roles for PAP-1 [4].

Recently R- and S-enantiomers of BEL were developed and validated to selectively inhibit Group VIB and VIA PLA$_2$, respectively [40,41]. The mechanisms involved in their selectivity are under study; however, they have similar IC$_{50}$'s in cells as racemic BEL (50:50 mixture of R- and S-BEL, 2–5 μM). R- and S-BEL have proven extremely useful as tools to distinguish between Group VIA and VIB [40-42]. However, they still may inhibit PAP-1 and should be used with propranolol when studying roles of Group VI PLA$_2$ in cell growth and signaling.

Several molecular techniques exist for inhibition and activation of Group VI PLA$_2$. Multiple studies have used siRNA or anti-sense oligonucleotides to inhibit Group VIA

PLA$_2$[11,13,21,42,43], as well as Group VIB PLA$_2$[42,44]. In addition, studies using mice null for Group VIA [45-47] have been published. To date no studies are available describing the use of knockout animals for Group VIB-F PLA$_2$.

In addition to knockdown studies, several studies have over expressed Group VIA and VIB PLA$_2$ and studied cellular function [34,48-50]. Relatively, few of these studies address the affect of Group VI PLA$_2$ over expression on cell growth or signaling. It should be noted that both Group VIA and VIB are constitutively active in several cell types. Thus, increasing Group VI PLA$_2$ activity may not have as great of consequence on cell growth or signaling as inhibiting its activity.

3. Group VI PLA$_2$ and cell growth and signaling

3.1. Evidence that Group VI PLA$_2$ mediate cell growth

Recent studies using both pharmacological and molecular inhibition strategies demonstrate that Group VI PLA$_2$ mediate growth, cell cycle regulation and signaling in a variety of models, and do so independently of Group IV PLA$_2$(Table 2, [9-12,42,51]). Models used in these studies include HEK293 cells, fibroblasts, macrophages, insulinomas, ovarian, colon, pancreatic and prostate cancer cells [9-11,13,23,51,52]. A majority of these studies focused on Group VIA PLA$_2$, although a significant amount of work focused on Group VIB PLA$_2$ as well [40,50,53].

Some of the first evidence that Group VI PLA$_2$-mediated cell growth was derived from studies in macrophages. For example, macrophage spreading was more effectively inhibited by BEL than MAFP, suggesting that Group VI PLA$_2$ have larger roles in macrophage growth than Group IV PLA$_2$[23]. This hypothesis was supported by subsequent studies in ovarian cancer cells [10,26], fibroblasts [54], smooth muscle cells [43], endothelial cells [55], HEK293 and Caki-1 cells [42], insulinoma cells [13,51] and colon cancer HCT116 cells [12].

Evidence that Group VI PLA$_2$ mediate cell growth is also derived from studies demonstrating that these enzymes regulate cell death. For example, inhibition of Group VI PLA$_2$ altered Fas-induced apoptosis in U937 cells [20,24], and chemotherapeutic-induced apoptosis in primary cultures of renal proximal tubules [53], HEK293 cells and Caki-1 cells [56]. Further, Group VI PLA$_2$ inhibition accelerated oxidant-induced necrosis in renal cells [17,57].

Group VIA PLA$_2$ is believed to be the primary isoform involved in Fas-induced apoptosis in U937 cells. In contrast, Group VIB PLA$_2$ appears to be more involved in mediation of renal cell apoptosis. This hypothesis is supported by studies demonstrating that expression of shRNA (plasmid forms or siRNA) against Group VIB PLA$_2$ increased lipid peroxidation and induced apoptosis in primary cultures of renal cells [44]. Further, renal cells appear to express higher level of Group VIB PLA$_2$, compared to Group VIA PLA$_2$[17,53,56].

3.2. Mechanisms by which Group VI PLA$_2$ regulate cell growth

While the above studies support the hypothesis that Group VI PLA$_2$ mediate cell growth, they do not identify the mechanisms or signaling pathways involved. It's possible, at least in some studies, that alterations in cell death alone can explain decreases in cell growth. However, several reports demonstrate that inhibition of Group VI PLA$_2$ decreases cell growth in the absence of cell death [9,10,12,42].

Inhibition of Group VI PLA$_2$ decreased prostate cancer cell growth in correlation with G1 and G2/M arrests, decreased EGFR activation and increased p53 expression [9]. Decreases in cell growth were not accompanied by increases in cell death as determined by annexin V and PI staining and nuclear morphology. This study confirmed early reports in HEK293 cells and human colon carcinomas, which demonstrated that inhibition of Group VIA PLA$_2$ increased p53 expression [11,12]. These studies also demonstrated that p53 induction increased the expression of p21, which induced G1 arrest. The mechanism of p53 induction may involve down regulation of the p53 antagonist mdm2 [9]. Further, Ma and co-workers demonstrated that inhibition of Group VI PLA$_2$-induced p53 via activation of ataxia-telangiectasia and Rad-3-related (ATR) kinase [12].

The above studies suggest that one mechanism by which Group VI PLA$_2$ mediate cell growth involves regulation of p53. However, studies in p53-null cells [9], or genetically modified cells lacking p53 [10], suggest that Group VI PLA$_2$ can mediate cell growth independently of p53. The signaling pathways involved are not exactly known, but may involve alteration of growth factors and cell stress signaling pathways such as EGFR and MAPK [9,10,43,58,59].

3.3. Group VI PLA$_2$ and EGFR

EGFR are integral membrane tyrosine kinases. They are members of the ErbB family of receptors, which contains four members. Upon activation, these receptors form dimers and recruit other proteins to their cytosolic domain [60]. Ligands that activate these receptors include neuropeptides like EGF, transforming growth factor-α (TGF-α), heparin-binding EGF-like growth factor (HB-EGF), amphiregulin, betacellulin, epiregulin and epigen [61]. GPCR ligands such as LPA also activate EGFR via transactivation mechanisms described below [62-71].

Two recent studies suggest that Group VI PLA$_2$ mediate the transactivation of EGFR in prostate [9] and ovarian cancer cells [10]. Other studies have suggested links between EGFR and PLA$_2$; however, most of these studies focused on Group VI PLA$_2$[63,65,72]. Inhibition of Group VI PLA$_2$ altered EGFR activation in both p53 positive and negative cells [9,10], suggesting that the ability of Group VI PLA$_2$ to regulate EGFR is p53-independent.

How exactly Group VI PLA$_2$ regulates EGFR is not known. EGFR transactivation can be dependent on GPCR and activation of PKC, presumably via activation of phospholipase C isoforms by Gα and βγ [71,73]. These signaling events, through unknown intermediate steps, result in the activation of membrane bound matrix metalloproteinases (MMPs), which cleave heparin-bound epidermal growth factor (HB-EGF) on the extracellular surface to release free EGF, which can in turn bind and activate EGFR [74,75] (Fig. 1).

Several potential sites of regulation for Group VI PLA_2 exist within the above pathway. First, the majority of the signaling molecules involved are either integral membrane proteins, or are associated with the membrane by lipid modification. Thus, the ability of Group VI PLA_2 to alter the plasma membrane lipid environment may alter the regulation of EGFR by GPCR, MMP or HB-EGF. More specifically, it has been clearly demonstrated that PKC can activate Group VI PLA_2[53,76]. Thus, Group VI PLA_2 may contribute to the missing link in the pathway between PKC activation and MMP activation.

3.4. Group VI PLA_2 and MAPK activation

Group VI PLA_2 may also mediate cell growth by regulating MAPK. Several studies demonstrate that Group VI PLA_2 inhibition alters MAPK activity. For example, treatment of rabbit ventricular myocytes with BEL inhibits thrombin stimulated p42/44 and p38 activation (two distinct types of MAPK) [59]. Activation of these MAPK appeared to be mediated by Group VI PLA_2-mediated release of LPC, and LPC exposure increased the activity of both p42/44 and p38.

It's also possible that Group VI PLA_2 regulate MAPK using arachidonic acid. Studies in vascular smooth muscle cells demonstrated that thrombin-induced DNA synthesis correlated to arachidonic acid release, which were both inhibited by BEL [43]. However, in contrast to data in ventricular myocytes, inhibition of MAPK, specifically p38, decreased Group VI PLA_2 activity, arachidonic acid release and DNA synthesis. These data suggest that the interaction of MAPK and Group VI PLA_2 are cell-dependent.

Another class of lipid signals that may mediate MAPK activation in tandem with Group VI PLA_2 is oxidized-low density lipoprotein (Ox-LDL). Ox-LDL result when reactive oxygen species oxidize the lipid constituents of LDL [77]. Ox-LDL induces p42/p44 in vascular smooth muscle cells using PKC and GPCR-mediated pathways [78]. Ox-LDL also induce MAPK p42/p44 and p38 in macrophages [79]. Few studies exist linking Group VI PLA_2 to Ox-LDL. The one study that could be found suggested that Ox-LDL activates Group VI PLA_2 and increases its expression in correlation with activation of MAPK [80].

4. Possible lipid signals by which Group VI PLA_2 regulate cell growth and signaling

A majority of the above studies demonstrate that alterations in EGFR and MAPK, as well as p53 and mdm2, occur downstream of Group VI PLA_2; however, these studies do not identify the signals involved. Like all PLA_2, Group VI PLA_2 can produce arachidonic acid and lysophospholipids [6,14,21-24], and recent studies even suggest roles in LPA production [25,26]. All of these lipids can mediate cell growth and signaling.

4.1. Group VI PLA_2, arachidonic acid, LPA and cell growth and signaling

Several studies demonstrate that inhibition of PLA_2 alters arachidonic acid and LPA release [1]. However, the majority of these studies focus on Group IV PLA_2. Further, many of these studies used MAFP or $AAOCF_3$. As mentioned above, these compounds decrease both Groups IV and VI PLA_2 activity [1,14,22,81]. Several recent studies demonstrate that

selective inhibition of Group VI PLA$_2$ using BEL, siRNA or anti-sense oligonucleotides, decreases cell growth, alters cell cycle and cell signaling [9-12,42,51]. While, these studies demonstrated direct roles for Group VI PLA$_2$ in cell growth, only one addressed the lipid signals involved [12].

Inhibition of Group VI PLA$_2$ may decrease the release of both arachidonic acid and LPA. This could decrease the basal activation of EGFR and MAPK, as well as GPCR pathways (Fig. 1). These events would decrease cell growth by a variety of mechanisms [1,6,82], the majority of which center around the downstream metabolism of each lipid. For example, arachidonic acid is metabolized by cyclooxygenases, lipoxygenases and cytochrome P450 monooxygenases to numerous compounds, most of which are known to induce cell growth [1], as well as EGFR and MAPK activation [59,63-66]. Lysophospholipids can be metabolized by lyso-phospholipase D (lysoPLD) to form lysophosphatidic acid (LPA). LPA activates GPCR-pathways, EGFR and MAPK in several cell types [69-71,83,84].

4.2. Alternative lipid pathways by which Group VI PLA$_2$ may mediate cell growth

Studies presented above suggest two hypotheses by which inhibition of Group VI PLA$_2$ alters cell growth (1) decreased arachidonic acid release and (2) decreased LPA production. It's also possible that the role of Group VI PLA$_2$ in cell growth is simply a result of its housekeeping function with regard to cellular phospholipids. This hypothesis is supported by studies in HEK293 and INS-1 cells, which demonstrate that inhibition of Group VIA and VIB PLA$_2$ altered several phospholipids in correlation with decreased cell growth and p53 activation [12,42,51].

A recent study demonstrated that Group VI PLA$_2$-mediated activation of p53 and cell cycle arrest correlated to increases in phospholipids containing poly-unsaturated fatty acids and decreases in those containing saturated fatty acids [12]. This study also demonstrated that direct addition of 18:2-phosphatidylcholine activated p53. This study suggests that Group VI PLA$_2$ inhibition alters cell signaling independently of either arachidonic acid or LPA.

Another Group VI PLA$_2$ metabolite that may mediate cell growth is LPC. As mentioned above, one of the primary functions of Group VI PLA$_2$ is to generate LPC acceptors. This LPC does not have to be generated from arachidonic acid containing phospholipids. Thus, inhibition of Group VI PLA$_2$ could decrease basal levels of LPC without altering arachidonic acid levels. LPC is suggested to play roles in cell signaling[6,51,82,85], which can be independent of it's conversion to LPA [6,82]. The mechanisms involved in LPC stimulated cell growth are not well understood, and few studies suggest roles for Group VI PLA$_2$ in LPC-mediated cell growth.

5. Roles for novel Group VI PLA$_2$ in cell growth

Almost all of the above studies focus on Group VIA or VIB PLA$_2$ in cell growth and signaling. In contrast, few studies exist addressing roles for Group VIC, VID, VIE and VIF PLA$_2$ in these same processes. Several functions for these newer Group VI PLA$_2$ are reported (see [4] for review). For example, Group VIC PLA$_2$ is also called neuropathy target esterase and may mediate membrane homeostasis in axons [4,19]. Group VID, VIE and VIF

PLA$_2$ all possess triacylglycerol lipase and acylglycerol transacylase activity and may mediate energy homeostasis [18]. Importantly, Group VID, VIE and VIF PLA$_2$ are all inhibited by BEL. This fact must be taken into account when attempting to identify the role of different Group VI PLA$_2$ in cell growth. It's clear that studies are needed examining the role of the newer Group VI PLA$_2$ in cell signaling and growth.

6. Summary and conclusions

Roles for Group VI PLA$_2$ in cell signaling and growth are becoming more apparent in several cell types. Several studies demonstrate that Group VI PLA$_2$ are more than just mere "housekeeping" proteins. The irony of this situation is that the housekeeping role of Group VI PLA$_2$ may be key to their ability to mediate cell growth. Their ability to function in the absence of Ca^{2+}, and comparatively lower selectivity for arachidonic acid, makes them suitable for controlling the level of several types of lipid signals under normal conditions.

It is important to note that few studies suggest that Group VI PLA$_2$ supplicates, or circumvents those of Group IV or the Groups that correspond to sPLA$_2$ (I–III, V, IX–XIV). Indeed, it appears that Group VI PLA$_2$ activity actually declines under conditions in which these later two enzymes are induced. For example high levels of ROS formation and lipid peroxidation inactivate Group VI PLA$_2$[57,86]. Yet, these same conditions can activate Groups IV and II PLA$_2$[87,88]. Thus, these enzymes appear to have distinct roles in cell growth and death.

The bulk of studies, addressing roles of Group VI PLA$_2$ in cell growth, signaling and death focus on one enzyme. This is almost out of necessity, and these studies are paramount to our understanding of the role of individual Group VI PLA$_2$ in these processes. Nevertheless, studies are needed addressing the differential roles of Group VI PLA$_2$ isoforms in cell growth and signaling in common models.

The ability of Group VI PLA$_2$ to mediate cell growth suggests that it may be a drug target in several pathologies including cardiovascular diseases, renal pathologies, atherosclerosis and cancer. This hypothesis is supported by the fact that many of these diseases are characterized by deregulated cell growth. For example proliferation of endothelial cells in atherosclerosis may be decreased by Group VI PLA$_2$ inhibitors. Further, the ability of Group VI PLA$_2$ inhibitors to decrease growth in cancer cells suggest that it may be a target for chemotherapeutic intervention [1]. Studies are needed correlating the activity and expression of Group VI PLA$_2$ to alterations in the above pathologies *in vivo*.

In closing, Group VI PLA$_2$ mediate growth and signaling in numerous cell types. As such, they may offer unique targets for treatment of a variety of pathologies whose etiology involves the generation of lipid signals. Future studies are needed focusing on alteration of Group VI PLA$_2$ expression and activity *in vivo* to realize this goal. Indeed, such studies are already underway using genetically modified animals lacking Group VIA PLA$_2$[45-47]. Studies are also needed developing permeable, non-toxic and selective Group VI PLA$_2$ pharmacological inhibitors for *in vivo* use.

Abbreviations

AAOCF₃	arachidonyl triflouromethylketone
BEL	bromoenol lactone ((E)-6-(1-bromoethyl) tetrahydro-3-(1-naphthalenyl)-2H-pyran-2-one))
cPLA₂	cytosolic phospholipase A_2
EGF	epidermal growth factor
EGFR	epidermal growth factor receptor(s)
GPCR	G-protein coupled receptor(s)
MAPF	methyl arachidonyl flourophosphonate
Ox-LDL	oxidized-low density lipoproteins
PAF-HA	platelet activating factor-acetylhydrolase
PLA₂	phospholipase A_2
PKC	protein kinase C
sPLA₂	secretory phospholipase A_2

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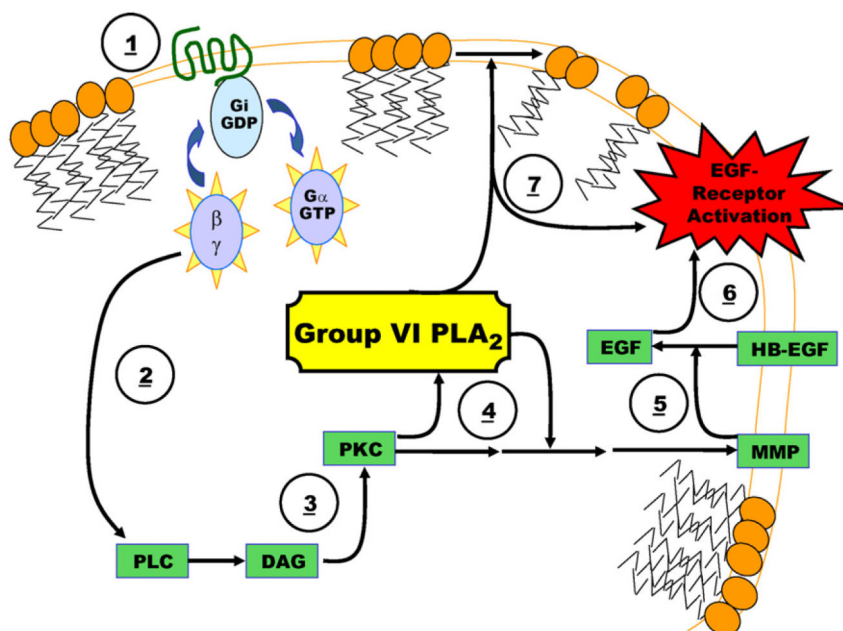
Fig. 1.

Proposed signaling pathways by which Group VI PLA$_2$ mediate cell growth. (1) Group VI PLA$_2$ may mediate G-protein coupled receptors (GPCR), such as those activated by lysophosphatidic acid (LPA), by either altering substrate generation for these receptors, or by altering the activity of their downstream targets. (2) GPCR activation results in the release of Ga and bg subunits, which can activate numerous signaling pathways, including phospholipase C (PLC). (3) PLC can produce diacylglycerol (DAG) and activate protein kinase C (PKC). (4) Interactions between PKC and Group VI PLA$_2$ are reported in several studies and may alter the activation of several downstream targets. (5) The targets of PKC include matrix metalloproteinase (MMP). (6) Alteration in MMP activity may alter the activation of epidermal growth factor-receptors (EGF-receptors) by altering the cleavage of heparin-bound-EGF (ProHB-EGF) to EGF. (7) Alternatively, EGF-receptors, GPCR and MMP are integral membrane proteins, or are associated with the membrane by lipid modification. Thus, the ability of Group VI PLA$_2$ to alter the signaling of these proteins may simply result from its ability to alter the plasma membrane lipid environment.

Table 1

Classification and inhibitors of Group VI PLA$_2$[a]

Group	Common name	Molecular weight (kDa)	Inhibitors	Suggested IC$_{50}$[b] (μM)
VIA-1	iPLA$_2$	84–85	AAOCF$_3$[c]	0.3/10
			MAFP	0.5/10
			S-BEL	
			BEL	0.5/5
VIA-2	iPLA$_2$β	88–90	AAOCF$_3$	0.3/10
			MAFP	0.5/10
			BEL	0.5/5
			S-BEL	1/2.5
VIB	iPLA$_2$γ	88–91	AAOCF$_3$	0.3/10
			MAFP	0.5/10
			BEL	0.5/2.5
			R-BEL	2/2.5
VIC	iPLA$_2$δ	146	BEL Organophosphorus esters	0.9/5 0.03-0.2/1-10
VID	iPLA$_2$ε	53	BEL	1–5
VIE	iPLA$_2$ζ	57	BEL	1–5
VIF	iPLA$_2$η	28	BEL	1–5

[a] Adapted from Cummings et al. (2007), and Schaloske and Dennis (2007).

[b] x/y: x = reported IC$_{50}$/y = dose commonly used in cells and tissues, when known.

[c] AAOCF$_3$ = arachidonyl triflouromethylketone; BEL = bromoenol lactone ((*E*)-6-(1-bromoethyl) tetrahydro-3-(1-naphthalenyl)-2H-pyran-2-one));
R-BEL = R enantiomer of BEL, S-BEL—S enantiomer of BEL, MAFP = methyl arachidonyl flourophosphonate.

Table 2

Cells in which Group VI PLA$_2$ mediates cell growth

Cell origin	Cell type	Reference
Cancerous		
Prostate	PC-3 and LNCaP	[9]
Ovarian	OVCAR-3, SKOV-3, DOV-13	[10]
Insulinoma	INS-1	[37,51]
Kidney	Caki-1	[42]
Colon	HCT	[11]
Fibroblast	3T6	[52]
Macrophages	Mouse peritoneal macrophages	[23]
Muscle	Rat vascular smooth muscle	[43]
Endothelial	HUVEC and HDMEC	[55]