Review

Structure, Function and Regulation of Group IV Phospholipase A_2 Family

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Abstract

The Group IV phospholipase A_2 family is consisted of six intracellular enzymes. They catalyze hydrolysis of the *sn*-2 ester bond of glycerophospholipids, releasing fatty acid metabolites and lysophospholipids. Agonist-induced release of arachidonic acid for the production of eicosanoids by PLA_2IValpha enzyme is important in regulating normal and pathological processes in a variety of target tissues. Here, we compare PLA_2IValpha, and its paralogs β, γ, δ, ε and ζ in term of of their structure, function and regulation.

Keywords: Group IV phospholipase A_2; cytosolic phospholipase A_2; arahidonic acid; C2 domain

1. Introduction

PLA_2s form a superfamily that currently contains 15 separate groups and numerous subgroups of PLA_2 as shown in table 1.[1,2,3] Enzymes are assigned to these groups based on sequence, number of disulfide bonds, molecular weight, calcium requirement, specific substrate and cell localization[3]. The superfamily of PLA_2 comprises a number of vary different proteins that can be divided into five principal kinds of enzymes, the small secreted PLA_2s (sPLA_2s), the cytosolic PLA_2s (cPLA_2s), the Ca^{2+}-independent PLA_2s (iPLA_2s), the Platelet-Activating Factor acetylhydrolases (PAF-AHs) and the lysosomal PLA_2s (LPLA_2s)[1]. These enzymes are characterized by their ability to specifically hydrolyse the sn-2 ester bond of phospholipid substrate, to produce free fatty acids and lysophospholipids, as shown in Fig. 1. Both products represents procursors for signaling molecules that can exert a variety of biological functions.[4]

This review aims to introduce the group IV of PLA_2 enzymes, their structure, biological function, regulation and role in pathophysiological processes, as well as focusing on one well defined mammalian enzyme called group IVA PLA_2 or PLA_2IValpha or cPLA_2α. With the completion of the mouse and human genomes it became clear that these mammals also contain other proteins homologous to cPLA_2α, namely the β, γ, δ, ε and ζ isoforms (groups IVB-F PLA_2s).[5,6]

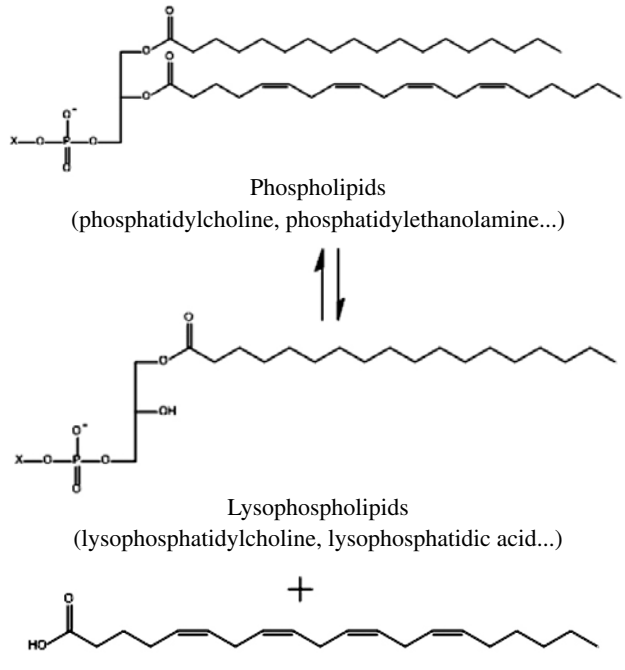

Fig 1: Chemical reaction catalyzed by the PLA_2 enzymes. Phospholipid is hydrolyzed at the sn-2 position to yield free fatty acids and lysophospholipids.

Tabele 1: Phospholipases A_2

Group	Source	Molecular Mass (kDa)	Type of enzyme
IA	Cobras and kraits	13–15	$sPLA_2$
IB	Human/murine	13–15	$sPLA_2$
IIA	Rattlesnakes	13–15	$sPLA_2$
IIB	Gaboon viper	13–15	$sPLA_2$
IIC	Rat/murine	15	$sPLA_2$
IID	Human/murine	14–15	$sPLA_2$
IIE	Human/murine	14–15	$sPLA_2$
IIF	Human/murine	16–17	$sPLA_2$
III	Human/murine	55	$sPLA_2$
IVA	Human/murine	85	$cPLA_2$
IVB	Human	114	$cPLA_2$
IVC	Human	61	$cPLA_2$*
IVD	Human/murine	92–93	$cPLA_2$
IVE	Murine	100	$cPLA_2$
IVF	Murine	96	$cPLA_2$
V	Human/murine heart/lung/macrophage	14	sPLA2
VIA-1	Human/murine	84–85	$iPLA_2$
VIA-2	Human/murine	88–90	iPLA2
VIB	Human/murine	88–91	$iPLA_2$
VIC	Human/murine	146	$iPLA_2$
VID	Human	53	$iPLA_2$
VIE	Human	57	$iPLA_2$
VIF	Human	28	$iPLA_2$
VIIA	Human, murine, porcine, bovine	45	PAF-AH
VIIB	Human, bovine	40	PAF-AH
VIIIA	Human	26	PAF-AH
VIIIB	Human	26	PAF-AH
IX	Snail venom (conodipine-M)	14	$sPLA_2$
X	Human spleen/thymus/leukocyte	14	$sPLA_2$
XIA	Green rice shoots (PLA2-I)	12.4	$sPLA_2$
XIB	Green rice shoots (PLA2-II)	12.9	$sPLA_2$
XII	Human/murine	19	$sPLA_2$
XIII	Parvovirus	<10	$sPLA_2$
XIV	Symbiotic fungus/ bacteria	13–19	$sPLA_2$
XV	Human, murine, bovine	45 (deglycosylated)	$LPLA_2$

* On the basis of sequence similarities, membrane bound group IVC PLA_2 is part of the cytosolic PLA_2s enzymes

2. Properties of Group IVA PLA_2 (PLA_2IValpha)

PLA_2IValpha plays a very important role in the release of arachidonic acid, a regulator of diverse cellular functions and a precursor for biosynthesis of potent inflammatory lipids such as eisosanoids, including prostaglandins, thromboxanes, leukotrienes and lipoxins[7]. PLA_2IValpha shows almost no homology with other PLA_2s. Among all PLA_2s, receptor-mediated arachidonic release is primarily attributed to PLA_2IValpha. It preferentially hydrolyses arachidonic acid from the *sn-2* position of membrane phospholipids in enzyme reaction that occurs in many cell types in response to varieties of extracellular stimuli[8,9,10]. PLA_2IValpha is on human chromosome 1 (mouse chromosome 1)[11]. It is highly conserved throughout evolution with human and mouse homologues sharing over 95% amino acid identity[10]. The homologues found in chickens, zebra fish and xenopus have over 80% amino acid identity with human PLA_2IValpha, consistent with an important conserved functional role. On the contrary, the mammalian Group IV paralogs PLA_2s β, γ, δ, ε and ζ genes are less conserved and share approximately 30–37% amino acid identity with PLA_2IValpha, suggesting different role in the cell.[5]

The PLA_2IValpha cDNA encodes a protein with a molecular weight of 85 kDa.[10] Primary structure of this enzyme starts with N-terminal calcium-dependent lipid binding domain (C2 or CaLB) followed by a catalytic domain (Fig. 2, Fig. 3).[10,12] The group IV PLA_2 family does not contain a classical lipase catalytic domain composed of a serine/acid/histidine triad. Instead, catalytic center is utilizing a conserved serine/aspartatic acid dyad.[12] Recent

kinetic study of PLA_2IValpha revealed that enzyme displays a PLA_1/PLA_2 specific activity ratio of 0.1 showing that it is PLA_2 enzyme. PLA_2IValpha displays relatively high lysophospholipase activity as well.[13] With the exception of PLA_2IVgamma all members of the group IV contain a C2 domain (Fig. 2). This hydrophobic C2 domain function to promote interaction of proteins with membranes.[14] It is composed approximately 120 amino acids that fold in an eight-stranded anti-paralel β-sheet. C2 domain binds 2-3 ions of calcium through aspartatic acid residues. Calcium binding neutralizes the anionic residues and favours PLA_2IValpha interaction with the membranes.[15]

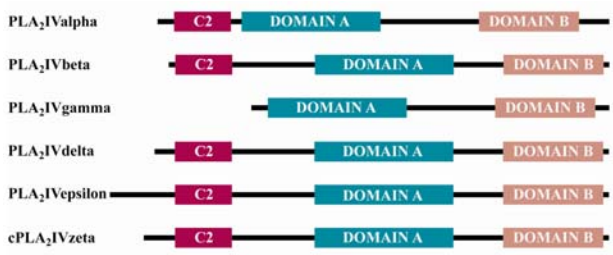

Fig 2: Shematical representation of primary structures of murine group IV of PLA_2 enzymes. Length of lines represents the polypeptide lengths, and boxes represent conserved domains with similarity within group IV of PLA_2s. C2 domain: calcium binding domain; catalytic domain A: the lipase consensus sequence, GXSGS, is located in its N-terminal; catalytic domain B: the lipase consensus sequence, DxG (except DTA in PLA_2IVepsilon).

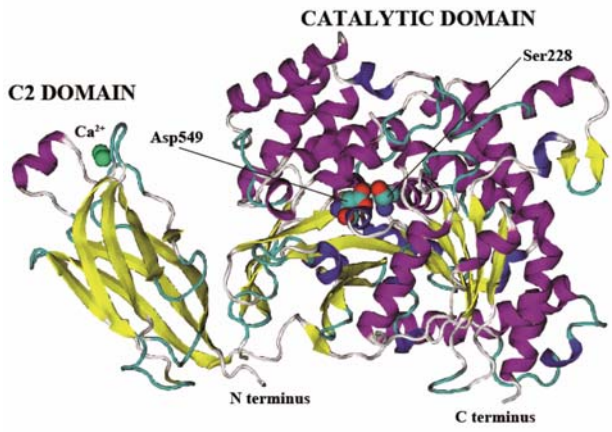

Fig 3: Structural features of human PLA_2IValpha. The cartoon diagram of human PLA_2IValpha shows α-helices (purple) and β-sheets (yellow). C2 domain binds two calcium ions (green) and promotes an enzyme to translocate from the cytosol to the membranes. In the catalytic domain, residues essential for catalytic activity including the Ser228/Asp549 dyad are shown in active site.

PLA_2IValpha is a widely distributed enzyme which is constitutively expressed in most cells and tissues.[8,16] Expression of PLA_2IValpha is increased by certain cytokines or inhibited by glucocorticoides.[8] Regulation of PLA_2IValpha by activators or signal transducers can involve effects on mRNA stability and transcription.[17,18] PLA_2IValpha is regulated by physiological levels of intracellular calcium concentration and phosphorylation by mitogen-activated protein kinase (MAPK)[10,19,20]. PLA_2IValpha is activated at submicromolar rather than millimolar calcium concentration[21,22]. Calcium binds to C2 domain and induces translocation of PLA_2IValpha from cytosol to the membranes of Golgi, endoplasmatic reticulum, nuclear envelope[23,24,25,26] and less frequently to the plasma membranes[27] or inside of the nucleus[28]. This is an important step in regulation of enzyme to access its substrate. However, translocation of PLA_2IValpha can occur without increase in calcium, indicating alternative regulatory mechanisms[23]. The MAPK family includes several subgroups including extracellular signal-regulated kinases, ERK1 (p44) and ERK2 (p42); c-Jun N-terminal kinases (JNKs) and p38. Agonist-induced phosphorylation of PLA_2IValpha at serine 505 by ERKs increases its catalytic activity and results in characteristic gel shift[19,26,29]. Although the PLA_2IValpha phosphorylation by ERKs[19,26,29] and p38[30,31,32] is well documented in the literature, only few reports indicate possible involvement of JNKs in PLA_2IValpha phosphorylation[32,33]. Beside PLA_2IValpha regulation by protein kinases and calcium, there is also evidence for direct association C2 domain with other binding proteins such as vimetin, which augments arahidonic acid release[34]. Activated receptors mediate signal via heterotrimeric GTP-binding (G) proteins to their effector enzymes, which include several phospholipases[19,35]. In particular, the G_o/G_i and G_q protein families have been shown to couple signaling to PLA_2IValpha[36,37]. Studies on dominant negative G_{i2} mutant demonstrated that inhibition of thrombin and ATP stimulated PLA_2IValpha mediated arachidonic release is MAPK and calcium independent, indicating possible direct coupling G-proteins with PLA_2IValpha[36,38]. We demonstrated that in CHO cells, the G_{12}/G_{13} family is also able to activate PLA_2IValpha, through the activation of RhoA and, subsequently, ERK1/2[39].

3. Properties of Group IVB PLA_2 (PLA_2IVbeta)

Human PLA_2IVbeta was cloned several years ago[40,41], but little is known about its structure, function and regulation. PLA_2IVbeta gene is located on chromosome 15. PLA_2IVbeta mRNA is expressed ubiquitously in human but more highly in cerebellum, heart, and pancreas[41]. More specifically, in rat cerebellum PLA_2IVbeta is localized in granule cells[42]. The form of PLA_2IVbeta cDNA encodes a protein with a predicted molecular weight of 114 kDa[40]. Catalytic and C2 domains of PLA_2IValpha and PLA_2IVbeta share about 30% amino acid identity. Human PLA_2IVbeta contains a unique N-terminal 242 amino acid extension upstream of the C2 domain that con-

tains a partial JmjC domain, but mouse PLA_2IVbeta does not. JmjC domains are predicted to be metalloenzymes that are often found in nuclear proteins and contain DNA and/or chromatin binding motifs, and regulate chromatin stability[43]. The truncated JmjC in PLA_2IVbeta would not be predicted to have a similar function since its structure is not complete. However, the truncated JmjC domain of PLA_2IVbeta may affect its membrane binding and/or catalytic properties although this remains to be determined. It is obvious that PLA_2IVbeta mRNA undergoes complex transcriptional and splicing regulation resulting in the production of functionally diverse protein products. PLA_2IVbeta was found to be expressed as a 100 kDa protein in human tissues and in a human lung epithelial cell line (BEAS-2B), not the 114 kDa protein originally predicted[44]. BEAS-2B cells contain three PLA_2IVbeta splice variants (PLA_2IVβ1, β2 and β3). All three transcripts contain the truncated JmjC domain and the C2 domain, but have differences in the catalytic domain. PLA_2IVβ1 is identical to the originally cloned form, whereas PLA_2IVβ2 and PLA_2IVβ3 contain internal deletions in the catalytic domain resulting in smaller proteins of 100 kDa. However, only PLA_2IVβ3 is translated into protein in BEAS-2B cells[44]. Although PLA_2IVβ3 exhibits calcium-dependent PLA_2 activity, it was found to be constitutively associated with membrane in BEAS-2B cells, and localizes to mitochondria and early endosomes[44]. PLA_2IVβ3 is widely expressed in tissues suggesting that it plays a generalized role at these organelles. A recent kinetic study of PLA_2IVbeta revealed that enzyme displays a PLA_1/PLA_2 specific activity ratio of 1.3 showing that it is a dual PLA_1/PLA_2 enzyme. PLA_2IVbeta displays relatively high lysophospholipase activity as well[13]. PLA_2IVbeta is an important metabolic enzyme not only in mammals but also in plants, where regulates light-induced stomatal opening in Arabidopsis[45].

4. Properties of Group IVC PLA_2 (PLA_2IVgamma)

Like PLA_2IVbeta, human PLA_2IVgamma was cloned several years ago[40,46] but little is known about its structure and function. PLA_2IVgamma gene is located on chromosome 19. Unlike PLA_2IValpha, human PLA_2IVgamma mRNA is not ubiquitous. PLA_2IVgamma mRNA is expressed most strongly in skeletal muscle and heart. The form of PLA_2IVgamma cDNA encodes a protein with a molecular weight of 61 kDa[40]. Human PLA_2IVgamma is 30% homologous to PLA_2IValpha and the residues necessary for PLA_2IValpha catalytic activity are conserved in PLA_2IVgamma[40]. PLA_2IVgamma lacks both the regulatory phosphorylation sites present in PLA_2IValpha and a C2 domain, but contains a prenyl group-binding site motif[46]. Farnesylation of C-terminal of the PLA_2IVgamma, together with palmitoylation[47] enhance protein hydrophobicity and most likely facilitate its localization to the endoplasmatic reticulum, Golgi apparatus[48] and mitohondria[47]. This calcium independent enzyme displays a PLA_1/PLA_2 specific activity ratio of 0.2 showing that it is mainly PLA_2 enzyme. PLA2γ also displays lysophospholipase activity on ^{14}C-P-LPC comparable to that of PLA_2IVbeta and PLA_2IValpha[13]. In some cases, PLA_2IVgamma may also function as a transacylase and consequently may play a role in phospholipid remodeling[49]. Furthermore, H_2O_2 and other hydroperoxides induce arachidonic acid release in PLA_2IVgamma, suggesting that it may be involved in metabolism of oxidative stress to repair oxidized phospholipids[50]. The arachidonic acid released by PLA_2IVgamma upon agonist stimulation is metabolized further to prostaglandin E_2 via cyclo-oxygenase-1 (COX-1) in the immediate response, and via COX-2 in the delayed response[48]. In bovine endometrial epithelial cells PLA_2IVgamma regulates prostaglandin E2 and F2alpha production upon oxytocin stimulation[51]. PLA_2IVgamma is also present in human retina, but its function remains unknown[52]. Epithelial PLA_2IVgamma accounts for the increased lysophospholipase activity observed during intestinal nematodiasis and it plays a major role in the inflammatory response to nematodes[53]. Interestingly, expression of mouse PLA_2IVgamma is restricted to the oocyte and early embryo, suggesting a unique role for mouse PLA_2IVgamma in early embryonic development[54].

5. Properties of Group IVD (PLA_2IVdelta)

Like PLA_2IVgamma, human PLA_2IVdelta was cloned several years ago[55]. PLA_2IVdelta gene is located on chromosome 15, near PLA_2IVbeta gene. PLA_2IVdelta mRNA is uniquely expressed in stratified squamous epithelium of cervix, fetal skin and prostate. cDNA of PLA_2IVdelta encodes a protein of approximately 90 kD and has greatest homology with PLA_2IVbeta, PLA_2IValpha and PLA_2IVgamma in the C2 and catalytic domain. Human PLA_2IVdelta has calcium-dependent release of arachidonic acid from 1-palmitoyl-2[^{14}C]arachidonoyl-phosphatidylcholine[55]. It displays a PLA_1/PLA_2 specific activity ratio of 5.3 showing that it is predominantly PLA_1 enzyme. PLA_2IVdelta also displays lysophospholipase activity on ^{14}C-P-LPC comparable to that of PLA_2IValpha, PLA_2IVbeta and PLA_2IVgamma[13]. In humans, PLA_2IVdelta may play a critical role in inflammation in psoriatic lesions[55]. Murine PLA_2IVdelta gene is located on chromosome 2, forms gene cluster with PLA_2IVbeta, PLA_2IVepsilon and PLA_2IVzeta gene. PLA_2IVdelta mRNA is in majority expressed in placenta, unlike the human homologue. The deduced amino acid sequence of PLA_2IVdelta revealed a C2 domain and catalytic domain. Murine PLA_2IVdelta is more homologous to PLA_2IVbeta

(41–50% amino acid identity in the catalytic domain and 33–43% identity in the C2 domain) than to PLA_2IValpha or PLA_2IVgamma (30–37% identity in the catalytic domain and 25–28% identity in the C2 domain). Recombinant protein demonstrated molecular weight of about 100 kDa and exhibited calcium dependent PLA_2 activity. Protein is enzymatically active but do not exhibit specificity for *sn*-2 arachidonic acid. PLA_2IVdelta translocates from cytosol to perinuclear sites in response to calcium ionophore[5].

6. Properties of Group IVE (PLA_2IVepsilon)

Human PLA_2IVepsilon has not been cloned yet. But like murine PLA_2IVdelta, murine PLA_2IVepsilon was cloned several years ago[5]. Murine PLA_2IVepsilon gene is located on chromosome 2, forms gene cluster with PLA_2IV-beta, PLA_2IVdelta and PLA_2IVzeta gene. PLA_2IVepsilon mRNA is predominantly expressed in thyroid, heart, testis and skeletal muscle. From the deduced amino acid sequence of PLA_2IVepsilon, C2 domain and catalytic domain has been determined. Both domains are more homologous to PLA_2IVbeta than to PLA_2IValpha or PLA_2IV-gamma, similarly as seen in murine PLA_2IVdelta. Recombinant protein demonstrated molecular weight of about 100 kDa. It requires calcium for its activity. Protein is enzymatically active but do not exhibit specificity for *sn*-2 arachidonic acid. PLA_2IVepsilon appears to be partly associated with lysosomes, but not with ER/Golgi or mitochondoria. Stimulation with ionomycin did not cause redistribution of PLA_2IVepsilon in cytosol[5]. Recently same synthetic genes coding for human PLA_2IVepsilon were prepared and kinetic studies on recombinant protein were determined. Enyzme displays only a PLA_1 specific activity, which is relativily low compared to other $cPLA_2$s. This human PLA_2IVepsilon has extremely low specific activity as a lysophospholipase on ^{14}C-P-LPC and as a PLA_2 on ^{14}C-PAPC vesicles[13].

7. Properties of Group IVF (PLA_2IVzeta)

Human PLA_2IVzeta has not been cloned yet. Like murine PLA_2IVdelta and PLA_2IVepsilon, murine PLA_2IVzeta was cloned several years ago[5]. Murine PLA_2IVzeta gene is located on chromosome 2 and it is part of a gene cluster containing PLA_2IVbeta, PLA_2IV-delta and PLA_2IVepsilon. PLA_2IVzeta mRNA is expressed in thyroid and stomach. Both, C2 domain and catalytic domain are more homologous to PLA_2IVbeta than to PLA_2IValpha or PLA_2IVgamma, similarly as seen in murine PLA_2IVdelta and PLA_2IVepsilon. Recombinant protein with a molecular weight of about 100 kDa requires calcium for its activity. Enzyme does not exhibit specificity for *sn*-2 arachidonic acid. It displays a PLA_1/PLA_2 specific activity ratio of 0.6 showing that it is predominantly PLA_2 enzyme. PLA_2IVzeta displays very high lysophospholipase activity on ^{14}C-P-LPC comparable to that of PLA_2IValpha, and PLA_2IVbeta[13]. PLA_2IVzeta is cytosolic in resting cells and does not translocate to membranes after addition of ionomycin in CHO-K1 cells[5]. PLA_2IVzeta exhibits specific activity, inhibitor sensitivity, and low micromolar calcium dependence similar to PLA_2IValpha but different sublocalization in mouse lung fibroblasts. In response to ionomycin, EGFP-PLA_2IVzeta translocated to ruffles and dynamic vesicular structures[56].

8. Physiological and Pathological Roles of $cPLA_2$

The PLA_2IValpha knockout mouse model has provided important information about its role in physiological processes and disease.[80] The normal phenotype of PLA_2IValpha-null mice suggested that this enzyme is not crucial for development and normal physiology[59]. However, when the mice were tested for various diseases, especially those involving inflammation, the symptoms were much milder than wild type mice. PLA_2IValpha-null mice showed a great reduction in lipid mediator production which led to resistance to ischemia–reperfusion injury[60], anaphylactic responses[61] acute respiratory distress syndrome caused by acid or endotoxin[62,63], bleomycin-induced pulmonary fibrosis[64], collagen-induced autoimmune arthritis[65], experimental allergic encephalomyelitis[66]. In tumorigenesis of small intestine, PLA_2IValpha may have a role in the expansion of polyps rather than the initiation process[67]. Concerning normal physiology, the loss of PLA_2IValpha causes some defects on the renal concentrating function, have ulcerative lesions in the small intestine, enlarged hearts and defects in female reproduction implicating PLA_2IValpha and its metabolites in regulating normal physiological processes[68,69,70,71,72,73] Activation of PLA_2IValpha is essential for thrombin induced smooth muscle cell proliferation, which might lead to pathological thickening of vascular walls in atherosclerosis[74.] There is very little published evidence on the role of PLA_2IValpha in animal models of atherosclerosis. But Wyeth suggests that apoE–/–, PLA_2IValpha ko mice showed a reduced atherosclerotic plaque burden[75]. There are also some reports on PLA_2IValpha which might play a role in severe asthma pathogenesis[76]. Recognition of the importance of the PLA_2IValpha in inflammatory diseases has made it a very attractive drug target. Two of the most promising drug candidates include the indole derivative inhibitors developed by Wyeth[77,78], which display anti-arthritic and anti-bone destructive action[79], and prevent experimental

autoimmune encephalomyelitis[80], and the 2-oxoamide inhibitors developed by Six[81] and McKew[82], which show potency in reducing inflammatory effects[82]. There is also a report on a series of ketone-containing compounds that are also potent inhibitors of PLA_2IValpha[83,84]. The Wyeth are developing a new PLA_2IValpha inhibitor, girapladib, for osteoarthritis but data are limited[75].

Among many PLA_2s, PLA_2IValpha plays a central role in the lipid mediator production in pathological conditions, and therefore, we propose that PLA_2IValpha can be a potential target for the development of a novel class of non-steroidal anti-inflammatory drugs. Different biochemical approaches in vivo[59] and in vitro[85,86,87] must be carefully used to elucidate the role of the group IV PLA_2 in normal and pathological physiology.

9. References

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Povzetek

Skupina IV fosfolipaz A_2 trenutno obsega šest encimov. Encimi katalizirajo hidrolizo *sn*-2 estrske vezi glicerofosfolpidov, pri čemer nastane maščobna kislina in lizofosfolipid. Največkrat je produkt hidrolize arahidonska kislina, ki se pretvarja v aktivne eikozanoide, ki imajo pomembno vlogo pri regulaciji celičnih procesov v različnih tarčnih tkivih. V tem prispevku si bomo pogledali strukturo, funkcijo in regulacijo encima PLA_2IValpha in jo primerjali z ostalimi predstavniki skupine IV fosfolipaz A_2, in sicer z β, γ, δ, ε and ζ.