Phospholipase A2: A Potential Therapeutic Target in Inflammation and Cancer (In silico, In vitro, In vivo and Clinical Approach)

Nagendra sastry Yarla*, Koduri Satyakumar1, Duppalapudi Srinivasu1, Kaladhar DSVGK1, Gjumrakch Aliev2,3, Gangappa Dharmapuri4,5,6

Abstract

Phospholipase A2 (PLA2) (EC 3.1.1.4) is the initial enzyme of arachidonic acid cascade, has key role in inflammation and cancer. Hence, PLA2 inhibitors have wide medicinal importance. This short review focused on PLA2 structure, function and role in inflammation and cancer. Further we tried to collect PLA2 inhibitors from the previous literature and explained the possibility of their utility as anti-inflammatory and anticancer agents.

Keywords: PLA2; Cancer; Inflammation; Therapeutic target

Introduction

Phospholipase A2 (PLA2) (EC 3.1.1.4) are group of enzymes, which specifically recognizes the sn-2 acyl bond of membrane bound phospholipids and hydrolyzes the bond releasing arachidonic acid and lysophospholipids. Upon downstream modification by cyclooxygenases and lipoxygenases, arachidonic acid is modified into prostaglandins and leukotrienes respectively. The same reaction also produces lysophospholipids, which represent another class of lipid mediators.

Biochemistry of PLA2

The enzyme is widespread in bacteria, plants, snake and bee venoms, and mammalian tissues and secretions. So far, at least 19 enzymes have been identified in mammalian tissues that possess PLA2 activity. Mammalian PLA2s are divided into various groups, namely, secretory (sPLA2), cytosolic (cPLA2), and Ca++-independent PLA2s, on the basis of their enzymatic properties and structures (Figure 1). The secreted PLA2(s) were the first type of PLA2 enzymes discovered. They are found in diverse sources including venoms from various snakes, scorpions, etc.; pancreatic juices components; arthritic synovial fluid; and in many different mammalian tissues. The intracellular PLA2(s) are grouped as cytosolic PLA2(s), which require calcium so called as Ca-dependent PLA(s). These phospholipases are involved in inflammatory response and carcinogenesis. The Ca dependent PLA, are characterized by not requiring Ca++ for catalytic activity. Platelet activating factor acetylhydrolases (PAF-AH) are called as GVII and GVIII PLA2(s), can catalyze the acetyl group from the sn-2 position of PAF to produce lysophosphatidyl ethanolamine. GVIII PLA2 involved in Lipoprotein metabolism so it is named as Lp-PLA2. Earlier studies suggest that Lp-PLA2 plays key role in the development and progression of atherosclerosis.

Lysosomal phospholipase A2 (GXV LPLA2) and Adipose specific phospholipase A2 (GVX1 ADPLA) are other types of the PLA2 superfamily (Figure 1) and don’t have any involvement in inflammation and carcinogenesis. 12 distinct groups of mammalian PLA2s are well characterized with many subgroups [1,2]. Some of the crystal structures of PLA2(s) are given in Figure 2.

cPLA2 and sPLA2 are commonly involved in arachidonic acid cascade. PLA2 is the initial enzyme of the arachidonic acid cascade, which has key role in inflammatory responses. Phosphorylation and calcium concentrations are the regulating the activity of PLA2. MAPK phosphorylates PLA2 at Serine-505 residue. When phosphorylation is coupled with an influx of calcium ions, PLA2 becomes activated and can translocate to the membrane for catalysis. Further, phosphorylation of PLA2 may be a result of respective ligand binding to receptors, including: IFN-a and y receptors, 5-HT2 receptors, basic fibroblast growth factor (bFGF). STRING is a popular database of known and predicted interactions.

*Corresponding author: Nagendra Sastry Yarla, Department of Biochemistry/ Bioinformatics, School of Life Sciences, GITAM Institute of Science, GITAM University, Visakhapatnam, A.P., India, Tel: +91-9701608894; E-mail: sastryyn@gmail.com

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predicted protein interactions and demonstrates the direct (physical) and indirect (functional) associations [3]. The functional protein network analysis (using String database) of PLA2 in Homo sapiens, which demonstrates the relationship between PLA2 and other enzymes or other functional proteins (5-LOX, COX and MAPK), which have key role in inflammation and cancer (Figure 3). MAPK signaling pathway is commonly involved in both physiological and pathological cell growth and proliferation. MAPK inhibitors would represent a novel class of anticancer agents. Fos and jun are proto-oncogenes, involved in carcinogenesis. PLA2(s) have been implicated in diverse pathological conditions, including inflammation related disorders and cancer. Elevated levels of sPLA2 and cPLA2 have been reported in cancer [4,5].

Role of PLA2 in Inflammation

Elevated PLA2 catalytic activities have been found in synovial fluid of patients, who suffered with rheumatoid arthritis, osteoarthritis, and crystal-associated arthritis. The PLA2-II enzyme is commonly present in synovial fluid in various arthropathies. Increased PLA2 activity is responsible marker for the inflammation in rheumatoid arthritis. Persistent subnormal amounts of PLA2 activity and concentration have been reported in patients with systemic sclerosis [6,7]. PLA2 activity in serum in sepsis and septic shock correlated with the concentration of synovial-type PLA2-II. But no correlation was found with pancreatic PLA2-I 8. Group PLA2-II concentration is increases in serum after extensive surgery and decreasing gradually thereafter. Postoperative group II PLA2 values correlate well with the concentration of C reactive protein in serum [8]. Zieve and Vogel firstly reported that increased PLA2 activity in serum in acute pancreatitis patients in 1961 [8]. The elevation of PLA2 was correlated with the severity of the disease [9,10].

Role of PLA2 in Cancer

Yamashita et al., found that PLA2 levels were highly elevated in patients with various malignant tumors, especially in breast cancer [11]. They also found elevated PLA2 mRNA levels in primary and metastatic site of the human breast cancer. Their study provides possible role of PLA2 in Breast cancer progression [11]. Human pancreas PLA2, designated hPLA2-1 (hPLA2-I), functions as a digestive enzyme. The active form of hPLA2-I stimulated the growth of a human pancreatic cancer cell line MIAPaCa-2 [12]. Group VI calcium-independent PLA(2) enzymes have also been recently implicated in carcinogenesis with in vitro studies suggesting the regulatory relationships amongst PLA2(2) enzymes, lipid mediator biosynthetic enzymes and the lipid mediators they produce during carcinogenesis [13].

cPLA2 have key regulatory roles in the invasive migration, proliferation, and capillary-like tubule formation of vascular endothelial cells as well as in tumor angiogenesis in mouse models of brain and lung cancer thus cPLA2 inhibition may be a novel effective antiangiogenic therapy [14].

Ovarian carcinomas express several PLA2, including high amount of cPLA2, but they do not contain type IIA 14 kDa sPLA2. On the contrary, neoplastic prostatic and gastric adenocarcinomas tissues showed positive immunostaining for secretory PLA2 [15]. The PLA2 activity in colon cancer tissues is much higher than normal colorectal mucosa. The results of subcutaneously injected cancer cells also support the role of PLA2 in colon cancer [15].

The earlier basic and clinical studies clearly demonstrated the role of PLA2 in cancer and inflammation thus the concept of PLA2 inhibition and decreased arachidonic acid availability still remains a good therapeutic approach for the treatment of inflammatory mediated diseases and cancer. Clinical studies results of cyclooxygenase or 5-lipoxygenase inhibition demonstrated the ineffectiveness in reduction of prostaglandins and leukotrienes (lipid mediators), but the inhibition of PLA2 results in reduction in both lipid mediators. The added advantage of PLA2 inhibition would be the reduction of Platelet Activating Factor (PAF) levels [16]. The key role of PLA2 in inflammatory related disorders and cancer thus makes the enzyme a potential target for drug development.

PLA2 inhibitors

PLA2 inhibitors have been isolated from natural sources including...
plants, microorganisms and marine associated organisms as anti-inflammatory and anticancer agents (Figure 4). Flavonoids, a group of secondary metabolites of plants have been reported for PLA2 inhibition. Rutin, is the glycoside between the flavonol quercetin and the disaccharide rutinose, widely distributed in plants. Rutin efficiently inhibited group II PLA2(s). Quercetin selectively inhibits the group II phospholipase A2 [17]. Flavanone and flavone O- and C-glycosides and methoxylated flavones are reporting a number of in vitro and in vivo anti-inflammatory and anticancer actions [18].

Manoalide is a potent anti-inflammatory sesterterpene isolated from a marine sponge in 1980. The anti-inflammatory activity of manoalide is due to inhibition of PLA2, through irreversible binding to some lysine residues of PLA2. Several manoalide analogs are also isolated and reported PLA2 inhibition activity. Manoalide 25-acetals were reported to possess in vivo antitumor activity. Scalaradine, marine associated metabolite was reported as PLA2 inhibitor [18-21]. Plastatin and luteosporin, have been isolated from fermentations of Penicillium chrysogenum as porcine pancreatic phospholipase A2 (PLA2) inhibitors [22]. Tetracycline’s are antibiotics from Streptomyces sp., which have been reported for PLA2 inhibitory activity [23]. Aristolochic acid is an alkaloid reported as potent PLA2 inhibitor, which are widely distributed in Aristolochia sp [24,25]. Coumestans (phytoestrogens) are a derivative of coumarin, are organic compound in the class of Flavonoids (polyphenols), isolated from Eclipta alba, which are reported as PLA2 inhibitor [26]. Ellagic acid (A), 3′-O-methyl ellagic acid (B), 3,3′-di-O-methyl ellagic acid (C), 3-O-methyl-3′,4′-methylenedioxy ellagic acid (D) were isolated from Casearia sylvestris SW (Flacourtiaceae) as PLA2 inhibitor [27]. 2-hydroxy-4-methoxy benzoic acid from Hemidesmus indicus root extract, which neutralized Russells’ viper venom induced lethal and haemorrhagic effects in experimental animals [20]. Rosmarinic acid was isolated from Cordia verbenacea (Boraginaceae) and reported as snake venom phospholipase A2 inhibitor. Further studies revealed that rosmarinic acid inhibits epidermal inflammatory responses and carcinogenesis [28,29].

Darapladib (N-[2-diethy laminoethyl]-2-[2-[(4-fluorophenyl)methyl sulfonyl]-4-oxo-6,7-dihydro-5H cyclopenta[d]pyrimidin-1-yl]-N-[(4-[trifluoromethyl]phenyl)phenyl)methyl]acetamide) is a lipoprotein-associated phospholipase A2 (Lp-PLA2) inhibitor that is in development as a drug for treatment of atherosclerosis, discovered by Human Genome Sciences in collaboration with GlaxoSmithKline (GSK). Darapladib had failed to meet endpoints of phase III in a trial of 16,000 patients with acute coronary syndrome. Further, trial of 13,000 patients failed to reduce the risk of coronary heart disease death [30,31]. LY333013 ([(3-Aminooxacyetyl)-2-ethyl-1-(phenethyl)-1H-indol-4-y]oxo[acetic acid) is sPLA2 inhibitor developed by Lilly Research Laboratories. In clinical trials, LY333013 showed greater reduction in swollen and tender joints than the placebo group of patients. In further clinical trial, LY333013 treated for 12 weeks, showed well tolerance but ineffective as an adjunct to disease-modifying antirheumatic drug treatment of active rheumatoid arthritis [32].

Conclusions and Future Directions
PLA2 is initial enzyme of arachidonic acid cascade. Previous reports demonstrated that PLA2 activity is high in various inflammatory conditions and cancer. Several PLA2 inhibitors have been reported as anti-inflammatory and anticancer agents. PLA2 enzyme is promising therapeutic target for inflammation and cancer even though, none of the PLA2 inhibitors are not available as drugs in market thus more investigation needed to discover novel PLA2 inhibitors as anti-inflammatory and anticancer agents.

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References


