Atlas of Genetics and Cytogenetics in Oncology and Haematology

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Gene Section
Mini Review

PLA2G4A (phospholipase A2, group IVA (cytosolic, calcium-dependent))

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Identity

Other names: CPLA2; MGC126350; PLA2G4; cPLA2-alpha

HGNC (Hugo): PLA2G4A

Location: 1q31.1

Local order: Centromere- PDC (phosducin), PTGS2 (prostaglandin-endoperoxide synthase 2), PLA2G4A (cytosolic phospholipase A2), FDPSL1 (farnesyl diphosphate synthase-like 1) -telomere.

DNA/RNA

Description

According to Entrez-Gene, human PLA2G4A maps to locus NC_000001.10. This gene contains 18 exons that encompass approximately 160 kb of genomic DNA. In mice, Pla2g4a maps to NC_000067.5 and contains 18 exons that span 131 kb of DNA within the mouse genome.

Transcription

Human PLA2G4A mRNA (NG_024420) consists of 2940 bp, and murine Pla2g4a mRNA (NM_008869) contains 2846 bp.

Pseudogene

No pseudogene has been identified for PLA2G4A.

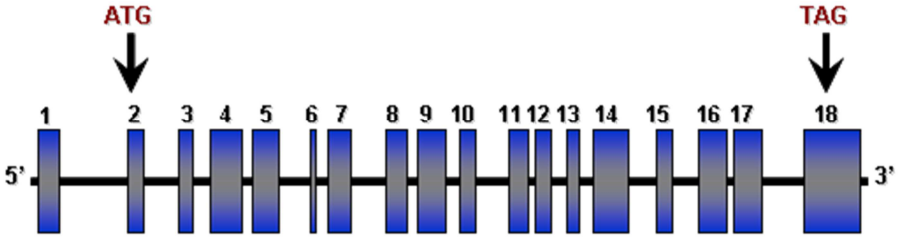
Protein

Description

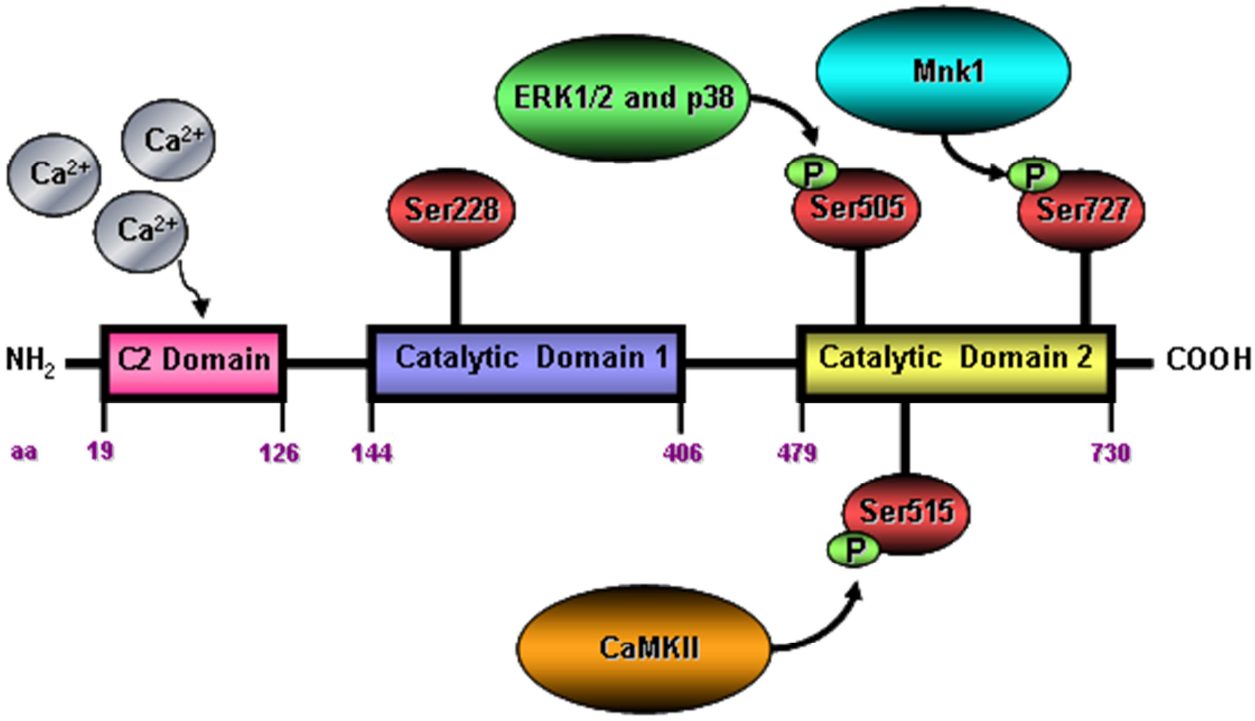
$cPLA_2$alpha is an 85 kDa protein consisting of 749 amino acids.

$cPLA_2$alpha belongs to the alpha-beta hydrolase family which is identified by a characteristic nucleophile elbow with a consensus sequence of Sm-X-Nu-Sm (Sm = small residue, X = any residue and Nu = nucleophile).

The protein contains an N-terminal C2 domain (Ca^{2+}-dependent, phospholipid binding) and two catalytic domains (alpha/beta hydrolase). The N-terminal region of the first catalytic domain contains the lipase consensus sequence, GXSGS. At the active site, $cPLA_2$alpha contains a serine nucleophile (Ser228) through which the catalytic mechanism is initiated.



PLA2G4A gene. PLA2G4A is comprised of 18 exons. The ATG start codon is located within exon 2 and the TAG stop codon is found in exon 18. The sizes of exons 1-18 are 135 bp, 101 bp, 81 bp, 148 bp, 113 bp, 37 bp, 141 bp, 136 bp, 222 bp, 114 bp, 137 bp, 92 bp, 71 bp, 242 bp, 184 bp, 195 bp, 157 bp, and 604 bp, respectively.



cPLA$_2$-alpha structure. The binding of calcium (Ca^{2+}) ions to the C2 domain promotes the translocation of cPLA$_2$alpha from the cytosol to the perinuclear/membrane region of the cell. Following this change in subcellular localization, cPLA$_2$alpha is phosphorylated on key serine residues by MAPKs (ERK1/ERK2 and p38), Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII), or MAPK-interacting kinase (Mnk1). Ser228 is located in the first catalytic domain and is critical for the enzymatic activity of cPLA$_2$alpha.

The active site is partially covered by a solvent-accessible flexible lid which spans from Arg413 to Gln457.

cPLA$_2$alpha displays interfacial activation as it exists in both "closed lid" and "open lid" forms. Upon membrane binding, gross conformational changes in the enzyme result in the movement of the cPLA$_2$alpha lid thus exposing a greater hydrophobic surface and the active site. This allows the fatty acyl chain of a substrate phospholipid molecule to enter the active site.

Expression

cPLA$_2$alpha is ubiquitously expressed throughout normal tissues, but is often overexpressed in human cancers.

Localisation

Prior to activation, cPLA$_2$alpha is localized to the cytoplasm. Upon an influx of intracellular calcium (Ca^{2+}), however, Ca^{2+} ions bind to the C2 domain and promote the translocation of cPLA$_2$alpha to either the nuclear envelope, Golgi apparatus, endoplasmic reticulum, or plasma membrane. The membrane-associated localization is then stabilized through the binding of the protein to anionic phospholipids or by phosphorylation of Ser505, Ser515, or Ser727. As a result of these molecular events, the enzymatic activity of cPLA$_2$alpha is increased.

Function

Following activation by Ca^{2+} concentration and/or phosphorylation, cPLA$_2$alpha hydrolyzes phospholipids at the sn-2-acyl ester bond to yield both free fatty acid as well as lysophospholipid second messengers.

Phosphatidylcholine (PC) is the most abundant phospholipid in mammalian cell membranes and is the primary target of cPLA$_2$alpha. The cPLA$_2$alpha-mediated cleavage of PC results in the release of arachidonic acid (AA) and lysophosphatidylcholine (LPC). AA is further metabolized to prostaglandins and leukotrienes by the cyclooxygenase and 5-lipoxygenase pathways, respectively. Thus, cPLA$_2$alpha and AA are key contributors to the inflammatory process. Lipid second messengers such as LPC and lysophosphatidic acid (LPA) are involved in downstream signal transduction that affects cell survival, proliferation, motility, and invasiveness.

Homology

Homologs of human PLA2G4A have been identified in the following organisms: Pan troglodytes, Canis lupus familiaris, Bos taurus, Mus musculus, Rattus norvegicus, Gallus gallus, Danio rerio. In addition, at least four paralogs of cPLA2 have been identified in mammals. They include cPLA$_2$alpha, cPLA$_2$beta, 2gamma, and cPLA$_2$delta. All paralogs contain the N-terminal C2 domain except cPLA$_2$gamma. Human cPLA$_2$gamma also harbors a myristoylation site at the N-terminus and is farnesylated at the C-terminus. The main residues that are essential to cPLA$_2$ catalytic activity (Arg200, Ser228, Asp549, Arg566) are conserved among all four paralogs of the enzyme.

Mutations

Germinal

In a study performed on 118 British family trios of schizophrenia patients, six single nucleotide polymorphisms (SNPs) were identified in the PTGS2/PLA2G4A locus. SNP4 was detected in the 5'-flanking region of the gene and was associated with elevated susceptibility to schizophrenia.
In a separate study of inherited prostanoid biosynthesis deficiency, a patient was found to possess three mutations of the PLA2G4A gene (S111P, R485H, and K651R). As a result of these mutations, the patient suffered from recurrent ulcerations of the small intestine and repeated episodes of gastrointestinal bleeding. Thus, such findings suggest that cPLA$_2$alpha is important for maintaining the integrity of the small intestine.

Somatic

Overexpression of cPLA$_2$alpha has been identified in a variety of cancers including Non-small cell lung cancer (NSCLC), cholangiosarcomas, esophageal cancers, and cancers of the colon and small intestine. In many cases of NSCLC, cPLA$_2$alpha expression is often associated with the presence of oncogenic Ras mutations.

Implicated in

Solid cancers

Disease
Non-small cell lung cancer, cholangiosarcoma, colorectal cancer, esophageal cancer, cancer of the small intestine, and ovarian cancer.

Oncogenesis
cPLA$_2$alpha has been shown to contribute to tumor progression through increased COX-2 production and the promotion of angiogenesis by arachidonic acid and LPC. Activation of cPLA$_2$alpha is also associated with increased resistance to radiation therapy among tumor vasculature. This resistance is often the result of cPLA$_2$alpha-mediated LPC generation and subsequent downstream activation of the PI3K/Akt and MAPK pro-survival signal transduction pathways.

Non-small cell lung cancer (NSCLC)

Note
Multiple studies have shown that cPLA$_2$alpha is frequently overexpressed in established NSCLC cell lines and tumor tissue samples from NSCLC patients. Overexpression of cPLA$_2$alpha resulted in increased levels of COX-2 as well as PGE$_2$. Both COX-2 and PGE$_2$ are associated with enhanced lung tumorigenesis.

Cholangiosarcoma

Note
Cholangiosarcoma is a tumor of the bile duct connective tissues that accounts for 10-15% of primary liver cancers. In this highly malignant tumor, a 5-fold increase in cPLA$_2$alpha mRNA has been reported. In addition, cPLA$_2$alpha has been shown to activate a nuclear receptor, peroxisome proliferator-activated receptor-delta (PPARdelta). Activation of PPARdelta accelerates the growth of human cholangiosarcoma.

Colorectal cancer

Note
Compared to normal colon tissue, cPLA$_2$alpha protein levels and enzymatic activity are often elevated as much as 50-60% in surgically excised human tumor tissue and established colon cancer cell lines. Increased cPLA$_2$alpha expression was positively correlated with enhanced COX-2 expression. COX-2 plays a vital role in the progression of colorectal cancer through its promotion of cellular proliferation, angiogenesis, invasion, and metastasis.

Esophageal cancer

Note
Esophageal cancer is the sixth-leading cause of cancer-related death in the world. With an 18% increase in cPLA$_2$alpha protein levels in tumor cells, recent reports have demonstrated that activation of the cPLA$_2$alpha/COX-2 pathway stimulates esophageal squamous-cell carcinoma cellular proliferation.

Tumors of the small intestine

Note
In vivo studies using cPLA$_2$alpha-deficient/APC^{Min} mice revealed that the size of small intestinal polyps was reduced by 11-fold compared to their cPLA$_2$alpha$^{+/+}$/APC^{Min} counterparts. The results also demonstrated an 83% reduction in the total number of intestinal tumors in cPLA$_2$alpha-deficient/APC^{Min} mice.

Ovarian cancer

Note
cPLA$_2$alpha is responsible for the production of lysophosphatidylcholine (LPC). However, LPC is frequently hydrolyzed to lysophosphatidic acid (LPA) which is a known stimulant of tumor cell proliferation, migration, invasion, and metastasis. A growing number of reports have shown that plasma LPA levels are elevated in ovarian cancer patients. In a study of 133 patients, women with ovarian cancer exhibited significantly higher LPA levels within their plasma (16.99 µM) compared to patients with benign ovarian tumors (7.73 µM) or patients with no ovarian malignancy (2.92 µM). Thus, cPLA$_2$alpha may serve as an important target for ovarian cancer therapy.

Other diseases

Disease
cPLA$_2$alpha has also been implicated in a variety of other diseases including cardiovascular disease, diabetes, asthma, and arthritis. In addition to these and other inflammatory disorders, cPLA$_2$alpha expression

is positively correlated with psychiatric disease states such as schizophrenia, Alzheimer's disease, and mood disorders.

To be noted

Recent data have shown that $cPLA_2$alpha may serve as a novel molecular target for anti-inflammatory agents, anti-angiogenesis therapy and tumor sensitization to radiation therapy.

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