Biochemistry, Phospholipase A2

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Introduction

Phospholipase A (PLA) comprises a supergroup of esterase enzymes present in all human cells that play a key role in mediating the production of free fatty acids and lysophospholipids from glycerophospholipids. These enzymes are important for regulating homeostasis and disease pathogenesis in every organ system based on their activation and involvement in inflammatory mediation. Over 30 isoforms of PLA have been identified to date and differ heavily in function, cofactor requirement, and size. The isoforms are classified into 6 main groups including cytosolic PLA, Ca-independent PLA, secretory PLA, lysosomal PLA, adipose-specific PLA, and platelet-activating factor acetylhydrolase. Within each of these groups, numerous subtypes have been identified. This article will focus on summarizing the key roles for each of the 6 PLA subtypes that have been studied.[1]

Fundamentals

PLA plays several important physiologic roles including the production of inflammatory eicosanoid compounds from arachidonic acid. These compounds have been studied to be involved in the pathogenesis of various inflammatory conditions including rheumatoid arthritis, atherosclerosis, various forms of cancer, cardiovascular disease, and other inflammatory diseases. The advent of pharmacological compounds that function as PLA inhibitors serves an exciting role in our future approach to treating various inflammatory conditions.[1][2]

Molecular

Secretory PLA

The molecular structure of secretory PLA consists of 6 to 8 disulfide bonds and uses a histidine/aspartate active site with a calcium cofactor for catalyzation. Activation of secretory PLA becomes increased in response to aggregation of substrates as opposed to interaction with monomers. This phenomenon is known as interfacial aggregation and consists of an interplay between electrostatic and hydropic interactions to facilitate the binding between secretory PLA and phospholipid membranes. The binding capacity depends on the functional ability of various aromatic amino acids, of which the most notable in function is tryptophan. Within this group, 10 primary subtypes have been identified.

Cytosolic PLA

The supergroup of cytosolic PLA consists of 6 members that each contain 749 amino acids and share other structural similarities. The activity of most forms of cytosolic PLA is dependent on intracellular calcium-binding that facilitates the action of the enzyme at the phospholipid membrane. Specifically, the enzyme works at the *sn-2* position of arachidonic acid. Cytosolic PLA has also been shown to act on micelle substrates. In contrast to its action at phospholipid membranes, its action on micelles does not require calcium activation.

Ca-Independent PLA

activation by calcium to facilitate their primary function. The enzyme consists of a 752 amino acid sequence that is speculated to be regulated by various mechanisms including binding of ATP, cleavage by caspase enzymes, and interaction with calmodulin.

Lysosomal PLA

Lysosomal PLA was named as such due to its studied localization to lysosomes within cells. It contains the characteristic catalytic amino acid triad consisting of aspartic acid, serine, and histidine that allows it to function as a phospholipase with acyl-transferase activity and specificity for the substrates phosphatidylethanolamine (PE) and phosphatidylcholine (PC) within lysosomes. The enzyme can function independently without direct interaction with calcium. However, its activity can be altered by the presence of calcium that interacts with other upstream or downstream compounds that regulate its activity.

Adipose-Specific PLA

Similar to lysosomal PLA, adipose-specific PLA exhibits calcium-independent activity toward PE and PC. However, it does not have acyltransferase activity. Increased activity of adipose-specific PLA results in arachidonic acid release as a precursor for prostaglandin E, resulting in decreased intracellular cAMP and decreased lipolysis. The net effect of increased enzymatic activity is increased adiposity through regulation of intracellular cAMP.

Platelet-Activating Factor Acetylhydrolase

This group of enzymes function independently of calcium and contain both an amino acid catalytic triad involving aspartic acid, serine, and histidine and a binding motif for lipases and serine esterases. These molecular structures allow the enzyme to interact with lipoproteins in plasma and act on their substrate, platelet activating factor (PAF). PAF is a powerful inflammatory mediator that has been shown to play a significant role in many inflammatory disease processes.[1][3][4]

Function

Secretory PLA

Secretory PLA has been studied and shown to serve a wide variety of functions in the body. The enzyme possesses strong antibacterial and antiviral activity against many gram-positive and gram-negative bacteria. The mechanism behind this activity involves penetration of the peptidoglycan cell wall by degradation of membrane phospholipids. The antiviral mechanism of secretory PLA involves inhibition of chemokine receptors which ultimately prevents viral entry into host cells. Another notable function of secretory PLA involves the initiation of inflammatory mediation by prostanoids and leukotrienes. This is accomplished by the degradation of arachidonic acid and subsequent conversion into bioavailable eicosanoid compounds. Secretory PLA has also been studied as playing a role in allergic and anaphylactic reactions through activation of mast cells and subsequent release of histamine.

Cytosolic PLA

The primary studied functions of cytosolic PLA depend on an increase in intracellular calcium that facilitates the translocation of the enzyme to intracellular phospholipid membranes around the nucleus. Binding of intracellular calcium to the enzyme allows this to occur by neutralizing anionic molecules in the enzyme and promoting hydrophobic interaction with membrane substrates. Once bound to the phospholipid membrane, many other enzymes help to regulate the activity of cytosolic PLA through phosphorylation. The main notable function of cytosolic PLA involves hydrolysis of arachidonic acid to promote metabolism of substrates in either the cyclooxygenase (COX) or lipoxygenase (LOX) pathways. The resulting compounds are biologically active eicosanoids that play a vital role in intracellular immunity. Cytosolic PLA has also been shown to play a role in stimulating a potent immunologic enzyme known as NADPH oxidase that produces superoxide compounds to eliminate pathogens. Other notable functions of cytosolic PLA include cell cycle regulation of G1 phase progression.

Ca-Independent PLA

The functions of Ca-independent PLA have been studied as playing an important role in normal cell homeostasis. It has been implicated as serving a role in the promotion of cell cycle progression and, paradoxically, apoptosis of cells depending on the target cell. Other studied functions of the enzyme include the

and smooth muscle, and neuroaxonal regeneration in response to injury.

Lysosomal PLA

Lysosomal PLA plays a significant role in the degradation of phospholipids within lysosomes. Most notably, its function and high levels of expression in alveolar macrophages allow for surfactant phospholipid degradation. This process prevents the accumulation of phospholipids within cells. Failure of proper enzymatic function leads to phospholipidosis with notable phenotypic features in knockout mice including splenomegaly and increased foam cell formation. Lysosomal PLA also plays an important immunological role through processing of lipid antigens and subsequent use by CD1 proteins for presentation to leukocytes. This role has been studied regarding pulmonary infection with *Mycobacterium tuberculosis*. Results indicate that lysosomal PLA plays an essential role in the formation of adaptive Th1 T-cell immunity to *M. tuberculosis*.

Adipose-Specific PLA

Adipose-specific PLA is categorized as a tumor suppressor in the body. The function of the enzyme in adipocytes is important to the regulation of lipolysis and prostaglandin production. Increased enzymatic activity results in the formation of prostaglandin E, which causes decreased intracellular cAMP and increased adiposity.

Platelet-Activating Factor Aacetylhydrolase

Macrophages predominantly synthesize platelet-activating factor acetylhydrolase in the body. Protein synthesis of the enzyme increases during the process of monocyte differentiation into macrophages. The enzyme has been shown to be more catalytically active in LDL particles rather than HDL particles, suggesting that their role in interacting with HDL may include a reservoir function when more enzyme is needed to interact with LDL. The body of evidence surrounding the proper function of platelet-activating factor acetylhydrolase has changed considerably over time. Initially, it was thought to play a key role in the prevention of the development of atherosclerosis; however, recent evidence suggests that its function is atherogenic. Therefore, the enzyme is now considered to be an independent risk factor for the development of atherosclerosis and coronary artery disease.[1][5][3][6]

Pathophysiology

Secretory PLA

Secretory PLA has been shown to play a significant role in the pathogenesis of many conditions that involve inflammation including rheumatoid arthritis, atherosclerosis, asthma, acute respiratory distress syndrome (ARDS), Crohn’s disease, ulcerative colitis, and tumor cell growth.

The pathophysiology of ARDS and asthma involve 2 mechanisms related to normal respiratory physiology. Normal expression of secretory PLA results in increased leukotrienes which serve as potent chemokines, resulting in leukocyte attraction and subsequent release of proinflammatory cytokines. This role has been established in the pathogenesis of asthma. Another mechanism that contributes more to the pathophysiology of ARDS involves secretory PLA degradation of the lung surfactants phosphatidylcholine and phosphatidylglycerol. This results in further respiratory inflammation and alveolar collapse.

The pathogenesis of atherosclerosis has also been correlated with increased expression of secretory PLA. The mechanism is proposed to involve hydrolyzation of phospholipids in LDL particles that results in macrophage uptake and subsequent intimal lipid accumulation. Studies have shown a positive correlation between blood levels of secretory PLA and coronary artery disease as a result of atherosclerosis of coronary vessels from oxidative damage.

Cytosolic PLA

Disturbance in the normal function of cytosolic PLA prevents the inflammatory response to take place. This results in resistance to a variety of inflammatory-mediated pathologies including anaphylaxis, rheumatoid arthritis, fatty liver disease, and acute respiratory distress syndrome. Cytosolic PLA has been studied as playing a noteworthy role in the pathogenesis of many forms of cancer including estrogen-depending breast cancer, adenocarcinoma of the lung, and glioblastoma multiforme. The effect of overactivity of the enzyme on many disease processes makes it a viable research target for disease intervention. One side effect noted in knockout mice with absent enzymatic activity included a reduced function of renal concentration.

Ca-Independent PLA

cells, resulting in the pathogenesis of diabetes mellitus. This occurs through the production of superoxide compounds by neutrophils that ultimately results in cell death. In contrast, failure of the enzyme to function under normal physiologic conditions has been associated with neuroaxonal dystrophy diseases with earlier onset.

Lysosomal PLA

Although not as well studied as other phospholipases, evidence suggests that failure of lysosomal PLA to function properly plays a role in atherogenesis and formation of phospholipidosis. From an immunologic perspective, impaired enzymatic function results in failure of pulmonary T-cell activation. This role has been studied in pulmonary tuberculosis infection in which mice deficient in the enzyme showed increased mycobacterial counts and decreased inflammatory response to infection.

Adipose-Specific PLA

Although designated as adipose-specific PLA, the enzyme has been shown to be expressed throughout many tissues, with the highest levels of expression occurring in adipocytes. The currently studied roles of the enzyme in the regulation of lipolysis and fatty acid oxidation make it a viable target for further research on obesity.

Platelet-Activating Factor Acetylhydrolase

As previously mentioned, the role of platelet-activating factor acetylhydrolase has been studied as playing a role in atherogenesis of blood vessels. This process has shown increased expression of the enzyme in association with oxidized LDL and inflammation, promoting the formation of atherosclerotic plaques. This studied function of the enzyme makes it a potential pharmaceutical target to prevent the progression of atherosclerotic disease.

Another studied pathophysiological mechanism involving platelet-activating factor acetylhydrolase includes neonatal necrotizing enterocolitis (NEC). This disease results in intestinal necrosis of premature infants. Low levels of the enzyme along with the accumulation of platelet-activating factor in newborns have been associated with the pathogenesis of the disease. These findings suggest that administration of exogenous forms of the enzyme may help to improve outcomes in NEC.[1][6][7][8][9]

Clinical Significance

Secretory PLA

Due to the well-known significance of secretory PLA in the pathogenesis of a wide variety of inflammatory disease processes, attempts at synthesizing inhibitors of the enzyme have been underway for quite some time for the treatment of asthma and atherosclerosis related to cardiovascular disease. Broad spectrum inhibitors of the enzyme such as varespladib have been shown to cause a substantial decrease in the size of atherosclerotic lesions and an increase in HDL in mice. These results indicate that the enzyme remains a viable target for the prevention and treatment of atherosclerosis and further research is needed to evaluate safety and efficacy in humans. Other research targets related to the enzyme may be shifted towards upstream or downstream enzymes in the same pathway to achieve similar results, such as peroxisome proliferator-activated receptors (PPAR).

Cytosolic PLA

Cytosolic PLA has received much attention as a target for pharmaceutical drugs being the most potent PLA enzyme studied as playing a pivotal role in inflammatory disease pathogenesis. A wide variety of cytosolic PLA inhibitors have been developed and studied regarding their efficacy in treating inflammatory diseases such as rheumatoid arthritis and inflammatory-mediated hyperalgesia. Clinical trials are necessary to validate the safety and efficacy of these experimental drugs in human subjects. Future studies are needed to evaluate the pharmacological targeting of this enzyme to affect cell cycle progression for the treatment of various cancers and proliferative glomerulopathies.

Ca-Independent PLA

Research regarding the clinical role in Ca-independent PLA inhibitors is much more limited than some of the other more well-studied forms of the enzyme. As further research explains the clinical significance of the enzyme, the development of pharmaceutical targets within the enzyme will become clearer. Of note, a recent study showing the efficacy of 2 Ca-independent PLA inhibitors in combination with traditional chemotherapeutic agents has been shown to be effective in inhibiting the development of some forms of ovarian cancer.

One notable studied function of lysosomal PLA involves activation of pulmonary T-cells in response to infection with Mycobacterium tuberculosis. This role warrants further investigation for the pharmacological treatment of tuberculosis. More research is needed to evaluate the role of enzymatic manipulation of lysosomal PLA on various other disease processes.

Adipose-Specific PLA

Knock-out mice that lack adipose-specific PLA were shown to exhibit a high rate of lipolysis and an increase in fatty acid oxidation within adipocytes. These findings suggest that pharmacological inhibition of normal enzymatic function may be used in the treatment of obesity.

Platelet-Activating Factor Acetylhydrolase

Due to its well-studied role in the pathogenesis of atherosclerosis, platelet-activating factor acetylhydrolase inhibitors have been studied regarding their efficacy in lowering the risk for cardiovascular events. One notable studied inhibitor in clinical trials includes darapladib, which yields promising results in prevention and attenuation of events related to coronary artery disease. [1][2][7][5][6]

Questions

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