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REVIEW

Human Secretary Phospholipase A2 Mutations and Their Clinical Implications

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Abstract: Phospholipases A2 (PLA_2s) belong to a superfamily of enzymes responsible for hydrolysis of the sn-2 fatty acids of membrane phospholipids to release arachidonic acid. PLA_2s are the rate limiting enzyme for the downstream synthesis of prostaglandins and leukotrienes that are the main mediators of inflammation. The extracellular forms of this enzyme are also called the secretary phospholipase A2 ($sPLA_2$) and are distributed extensively in most of the tissues in the human body. Their integral role in inflammatory pathways has been the primary reason for the extensive research on this molecule. The catalytic mechanism of $sPLA_2$ is initiated by a histidine/aspartic acid/calcium complex within the active site. Though they are known to have certain housekeeping functions, certain mutations of $sPLA_2$ are known to be implicated in causation of certain pathologies leading to diseases such as atherosclerosis, cardiovascular diseases, benign fleck retina, neurodegeneration, and asthma. We present an overview of human $sPLA_2$ and a comprehensive compilation of the mutations that result in various disease phenotypes. The study not only helps to have a holistic understanding of human $sPLA_2$ mutations and their clinical implications, but is also a useful platform to initiate research pertaining to structure–function relationship of the mutations to develop effective therapies for management of these diseases.

Keywords: secretary phospholipase A_2, $sPLA_2$, mutations, clinical implications, structure–function relationship

Phospholipase A_2

Phospholipase hydrolyzes phospholipids into fatty acids and other lipophilic substances. The phospholipases are divided into groups depending on which glycerol ester bond they are capable of cleaving (these bonds are marked in Figure 1). The phospholipases are thus called phospholipase A, B, C and D. For phospholipase A, a subscript 1 or 2 is added depending on whether the cleaved bond involved is at the sn-1 or sn-2, position of the phospholipid substrate.[1] [1] Phospholipase B cleaves at both sn-1 and sn-2 positions. This is demonstrated by a diagrammatic illustration in Figure 1.

The discovery of PLA_2 was based on the observation that pancreatic juice and cobra venom were able to hydrolyze phosphatidylcholine (PC).[2] PLA_2 are major constituents in mammalian tissues as well as in insect and snake venoms. They are widespread in living organisms both as intracellular and extracellular forms and are the most extensively studied among all phospholipases. Phospholipases A_2 (PLA_2s, EC 3.1.1.4) are upstream regulators of many inflammatory processes which hydrolyze phospholipids at the sn-2 position of the glycerol backbone, releasing lysophospholipids and fatty acids.[1] They hydrolyze various naturally occurring

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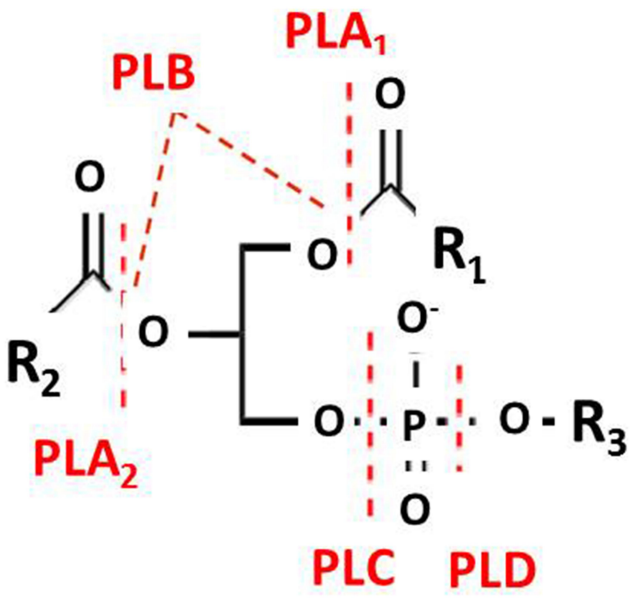

Figure 1 Diagrammatic representation showing the chemical bonds on the phospholipid substrate that are cleaved by the enzymes in the phospholipase family.

phospholipids such as phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, phosphatidylinositol, phosphatidylglycerol, plasmalogen, plasmenylcholine and 1-alkylether phosphatidylcholine and release the arachidonic acid. Upon downstream modification by cyclooxygenases, arachidonic acid is modified into active compounds called eicosanoids, which include prostaglandins, thromboxanes and leukotrienes which are categorized as inflammatory mediators which lead to pharmacological interest in this reaction.[1] Mammalian PLA_2 enzymes play an important role in the maintenance of the cellular phospholipid pools and membrane repair through deacylation/reacylation pathways and biosynthesis of prostaglandins and leukotrienes.[3]

PLA_2s are classified into 15 groups due to the advent of genomics which has seen an increase in the number of PLA_2 subgroups, leading to the characterization of exciting new PLA_2s.[4,5] Additional forms of secreted PLA_2 s ($sPLA_2$s) utilizing a catalytic histidine have been discovered in recent years, which are clearly related to the GI, GII, and GIII PLA_2, but do not easily fit into these groups. This led to the establishment of groups V, IX, X, XI, XII, XIII, and XIV. PLA_2s using serine as catalytic residue, cytosolic PLA_2s ($cPLA_2$s) were classified into GIV and Ca^{2+} independent PLA_2s ($iPLA_2$) formed GVI. PLA_2 s using the serine/histidine/aspartate triad in catalysis, platelet-activating factor acetylhydrolases (PAF-AH) forms GVII and GVIII, and the recently discovered lysosomal PLA_2s forms GXV. This review highlights the salient features of $sPLA_2$s and the effect of their mutations on clinical phenotypes.

Structure of Secretary PLA_2

Secreted PLA2 ($sPLA_2$) family bags more than one third of the isoforms. The family contains 11 calcium dependent isoforms (IB, IIA, IIC, IID, IIE, IIF, III, V, X, XIIA and XIIB) in mammals.[6] The secretory PLA_2s are characterized by relatively low molecular weights (typically <20 kDa) proteins. Groups III and XII, are structurally distinct from rest of the members of the group based on the protein sequence identity.[7] $sPLA_2$s have some common structural elements that include a conserved CCXHDXC motif with His-Asp catalytic dyad at the active site, a highly conserved calcium binding domain and extensively conserved disulfide-stabilized tertiary structure (Figure 2). The core conformation of $sPLA_2$ includes three α-helices, two anti-parallel β-strands, calcium binding loop, and a substrate binding hydrophobic channel. Few of the $sPLA_2$s, like in the human group III, isoform have a C-terminal extension.[7] Some of the characteristic structural features of $sPLA_2$ is highlighted in the following sections.

$sPLA_2$ GI/II coordinate the essential Ca^{2+} through a conserved and conformationally flexible loop of residues with the consensus sequence Y25-G-C-Y/F-C-G-X-G-G33 which contributes three closely spaced backbone carbonyl oxygens (O28, O30 and O32).[8] These carbonyl oxygen atoms, along with oxygen atoms donated by the carboxylate of Asp49 and two water molecules, form a tight pentagonal bipyramidal coordinate cage for the calcium ion. An analogous arrangement is found for the human GIII PLA_2 enzyme, where Trp9, Gly11 and Gly13 contribute the backbone carbonyls and the carboxylate group from Asp36 form the coordinate cage around the calcium ion.[7] Calcium coordination stabilizes the loop which otherwise has conformation that is flexible, to form the left-superior wall of the hydrophobic channel and orders the local protein structure in a manner that appears to optimize substrate interactions.

$sPLA_2$s contain three spatially conserved α-helices. Two long anti-parallel helices are riveted together by twin disulfide bridges to create a rigid backbone brace that forms the back wall of the substrate-binding pocket. Disulfide bridges found in $sPLA_2$s incorporate half-cysteines derived from this substructure. Conserved side-chains arising from the anti-parallel helices assist in the coordination of Ca^{2+} form the deeper contours of the

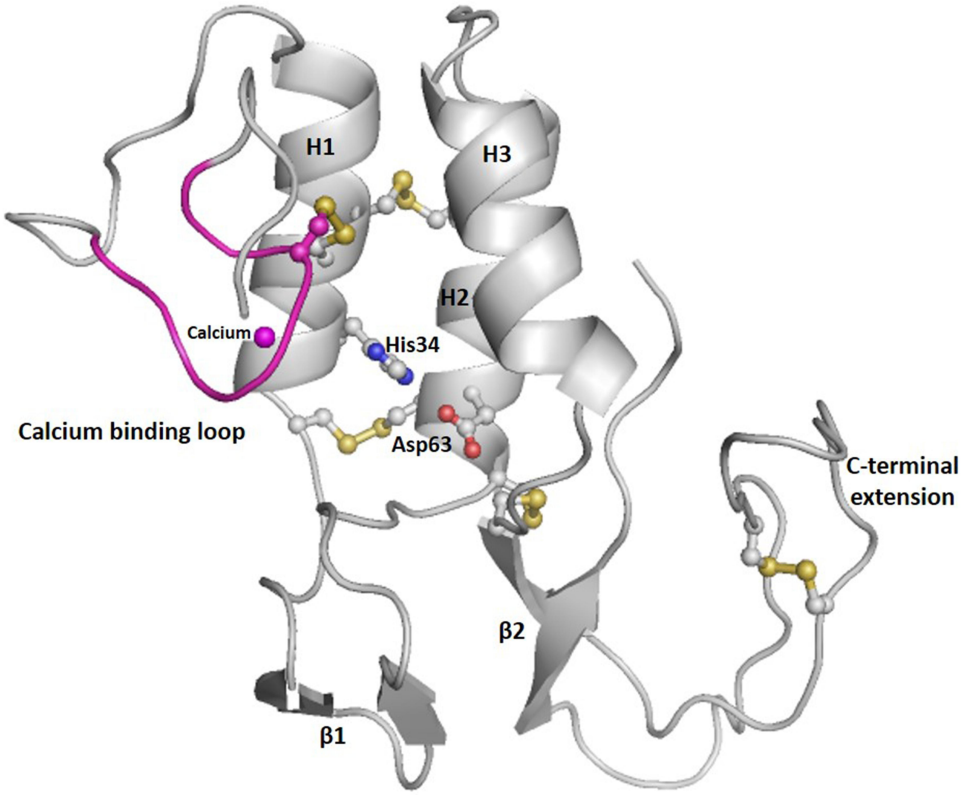

Figure 2 Ribbon diagram showing the overall structure of human group III PLA_2, a prototype human $sPLA_2$. Structure comprises of three helices, indicated as H1, H2, and H3; two β-wings, indicated as β1 and β2; calcium binding loop (pink) with the calcium ion (sphere in magenta); active site with residues histidine 34 and aspartic acid 63; C-terminal extension; and stabilized by five disulfide bonds (yellow). The structure was done using homology modeling on human group III PLA_2 sequence (Q9NZ20), and viewed on Pymol.

hydrophobic channel and creates a catalytic network comprising of histidine, aspartic acid, and tyrosine, which ensures fixed active site geometry.

In GI PLA_2s there is a distinctive loop of surface exposed residues arising from the distal tip of the first antiparallel helix. This loop is absent in GII enzymes, moderately developed among the GI elapids and most prominent among the GI enzymes from exocrine pancreas. There is little three-dimensional homology among $sPLA_2$ s in the region despite the presence of a conserved disulfide bridge (Cys61–Cys91). Deletion of residues 62–66 from the porcine pancreatic $sPLA_2$ improves activity on micellar zwitterionic lecithins by up to 16-fold.[9] This effect is likely to reflect the formation of a more favourable surface for interfacial adsorption.

All $sPLA_2$ structures contain either one (GI/II) or two (GIII) well-developed β-wing(s). This substructure consists of a single loop of anti-parallel β-sheet that extends outwards from the molecule into the bulk solvent. The distal portions of these substructures are poorly anchored and may adapt a variety of orientations with respect to the enzyme proper. In some enzyme species the composition of the β-wing may confer ancillary pharmacological properties such as anti-coagulation.[10]

The C-terminal extension of GII enzymes forms a semicircular barrier around the Ca^{2+}-binding loop. It is secured proximally (Cys126– Cys27) and distally (Cys134– Cys50) by disulfide bridges. The seven- or eight-residue loop is rich in proline and charged residues. In the human GIII $sPLA_2$, despite the fact that all the functional motifs of the enzyme are within the first hundred residues, there is an additional 42-amino acid that adapts a long loop conformation. This last part of the loop is in close proximity to the third helix and the overall compactness of the enzyme is thereby maintained.[11] This substructure is remote from the residues implicated in interfacial adsorption, substrate binding, and catalysis.[11] This is in contrast to heterodimeric structural variants of group III *s*PLA_2 from scorpions, wherein a single enzyme transcript codes for three distinct products that include a large enzymatic subunit, a pentameric peptide and a small non-enzymatic

subunit.[12,13] The enzymatic subunit comprises of three helices, the calcium binding loop and a substrate binding hydrophobic channel, and the non-enzymatic subunit comprises of extensive hydrophobic residues with a conformation of an anti-parallel β-sheets making it ideal for tissue specific targeting.[12]

This stereochemical mechanism of $sPLA_2$ is reminiscent of the catalytic system of the serine proteases.[14] A conserved water molecule acts as the attacking nucleophile attacks the sn-*2* bond. A conserved histidine in the active site of PLA_2 abstracts a proton from the water molecule at the Nδ1 position. The positive charge acquired by the histidine is stabilized through an extended hydrogen-bonded network that includes the carboxylate group of aspartic acid and the phenolic group tyrosine residues. It may be noted that the invariant aspartate and tyrosines at the active site are from nonanalogous backbone positions in different groups of the $sPLA_2$ enzymes. The histidine, aspartate and the single/dual tyrosine residues are rightly called as catalytic residues of the $sPLA_2$. It is noteworthy that this pattern of catalytic machinery is consistent in most groups of the $sPLA_2$ ranging from group I, II IV, V, X, and XII.[15–18] In the human group III *s*PLA_2 (human), there is a phenylalanine at the active site where its aromatic ring fails to make any hydrogen bonded interactions with either the histidine or the aspartate which are in its vicinity. It is therefore established that tyrosine is not an essential requisite for the stabilization of the aspartic acid residue at the active site of PLA_2 for its functionality.[7] Interestingly, $sPLA_2$ from the liver fluke parasite show classical features of histidine-aspartic acid-tyrosine in hydrogen bond formation at the active site.[19] This difference at the active site between the target enzyme and the housekeeping human isoform is, therefore, an important structural parameter that can be exploited to design-specific drug molecules against the parasite *Clonorchis sinensis*.[20]

Unlike several $sPLA_2$s in reptiles and scorpions that exist in solution as stable multichain complexes in the form of homodimers, homotrimers and heterodimers, native human $sPLA_2$s do not have quaternary conformations.[21,22] The human GIII $sPLA_2$ has a C-terminal extension that is reminiscent of the non-enzymatic subunit of a $sPLA_2$ from a scorpion that is associated with main enzymatic subunit by a disulfide bond.[12,13] However, ligand associated mutimerization is known wherein bisindole compounds and anionic molecules induce dimers in certain $sPLA_2$s.[23,24]

Physiological Functions of $sPLA_2$

The functions of PLA_2s go beyond their role in membrane homeostasis and they also function in such diverse roles such as digestion of nutrients to the formation of bioactive molecules involved in cell regulation. There are indications that a few phospholipases may carry out a biological function independent of their catalytic activity by binding to a regulatory membrane receptor. Phospholipase-like proteins with toxic properties, yet which lack a functional catalytic site, are found in venoms. It is of interest that most, but not all, phospholipases studied in detail thus far are soluble proteins. The soluble nature of many phospholipases suggests that their interaction with cellular membranes is one of the regulatory mechanisms that exist to prevent membrane degradation or to precisely control the formation of phospholipid-derived signalling molecules. In addition to the well-established functions of one of the $sPLA_2$ enzymes in digestion of dietary phospholipids and another in host defense against bacterial infections, accumulating evidence shows that some of these $sPLA_2$s are involved in arachidonic acid release from cellular phospholipids for the biosynthesis of eicosanoids, especially during inflammation.[4,25] $sPLA_2$s have also been involved in physiological and pathophysiological conditions in skin.[26]

PLA_2s as Mediators of Inflammation

PLA_2s participates in the inflammatory reaction in several different ways. PLA_2s liberates free fatty acids and lysophospholipids by their hydrolytic action on phospholipids that are found in membranes. In inflammation, AA is the key fatty acid liberated from phospholipids by PLA_2 s. This reaction regulates the availability of AA which, in turn, is the rate limiting precursor for the formation of prostaglandins.[25] AA is also the precursor of leukotrienes which are formed via the lipoxygenase pathway. The turnover of lysophospholipids in some conditions results in the formation of the platelet activating factor (PAF) which is another potent mediator of inflammation.[27] Platelet activating factor-acetylhydrolases (PAF-AH) is an enzyme that is essential for this reaction. There are four members of this family, of which three are intracellular, and the fourth member, the plasma PAF-AH, is secreted extracellularly. The structure of plasma PAF-AH enzyme is a member of the serine-dependent class of $sPLA_2$s. This enzyme has therefore been considered for discussion here.

Around 70–80% of circulating PAF-AH (Lp-PLA$_2$) is bound to low-density lipoprotein (LDL) and the remainder is linked to high density lipoprotein (HDL) and some very low-density lipoproteins. The two α helices help the enzyme associate with these lipoproteins. Low density lipid has affinity in the region between residues 114 and 126 while high density lipid is associated with the residues 362 to 369 of the two α helices. The enzyme possess a classic lipase α/β- serine hydrolase fold and a catalytic triad consisting of Ser273, Asp296, and His351. Ser273 is located on the N-terminus of an alpha helix and on the conserved motif GXSXG classical to other lipases and serine esterases. Ser273 is a nucleophilic residue activated for catalysis through other two residues—Asp296 and His351. Residues Leu153 and Phe274 serve as oxyanion hole and stabilize the negative charge of tetrahedral intermediate through their amide nitrogens. The catalytic triad is oriented within a hydrophobic pocket and positioned towards its lipid substrate. PAF is a phospholipid-signaling molecule that binds its specific receptor leading to a cascade of proinflammatory signals; thus, PAF is a prominent pro-inflammatory mediator.[28]

Certain sPLA$_2$s regulate a variety of biological functions through certain receptors called as sPLA$_2$ receptor.[29] These receptors are mannose type transmembrane glycoproteins that are related to the C-type animal lectin family. Some of the important receptor mediated functions are: (1) group X sPLA$_2$-receptor interaction for arachidonic acid release from spleen cells;[30] (2) group IB sPLA$_2$-receptor interaction for cell proliferation and lipid mediator production;[31] (3) group V sPLA$_2$-receptor interaction for proangiogenic and anti-angiogenic factors by human neutrophils;[32] (4) group I-receptor interaction for prostaglandin E2 production;[33] (5) group IV-receptor interaction for cytokine release.[34] In addition to physiological functions, the sPLA$_2$-receptor interactions are also implicated in causing certain diseases including cancer.[35,36]

Human sPLA$_2$ Mutations and Their Clinical Implications

sPLA$_2$ are expressed in different tissues of the human body.[37] In addition to its role in inflammation, they also known have a housekeeping role in some of these tissues.[38] Mutations on these sPLA$_2$ have an impact on the structure–function relationship of these enzymes that have various clinical implications. The various mutations on human sPLA$_2$ and their clinical fallouts have been given in Table 1.

sPLA$_2$ Mutations and Coronary Artery Diseases

Platelet-activating factor acetylhydrolase (PAF-AH) is a calcium independent secreted enzyme that is classified as sPLA$_2$, and associates both with LDL and HDL in human plasma.[5] It acts on the sn-2 position of the glycerol backbone of the biologically active lipid messenger PAF molecule causing its deacetylation to an inactive lyso-PAF, a product that is no longer recognized by the PAF receptor.[39] The PAF-AH activity may be considered anti-inflammatory and anti-atherogenic.[40] Apart from PAF, the enzyme due to its broad substrate specificity also hydrolyzes phosphatidylethanolamine (PE) and phosphatidylcholines (PC) with short chain sn-2 moeties to generate oxidized fatty acid and lysophosphatidylcholine, which are pro-inflammatory, procalcifying and proapoptotic lipid mediators.[41–44] These mediators play an important role in atherosclerotic plaque inflammation and development of atherosclerotic necrotic cores.[45] The products of these two separate enzymatic reactions have varying effects on plaque formation in coronary arteries thereby leading to pro-atherosclerotic and anti-atherosclerotic clinical phenotypic outcomes.[40,46-50] The varying clinical effects seen by effect of PAF-AH enzyme is probably due to the following reasons: (1) varying expression of the substrates; (2) varying affinity of the enzyme towards these substrates; and (3) varying enzyme kinetics leading to differential product concentrations that dictate the molecular pathogenesis.

It is clear from the above discussion that mutations on the enzyme PAF-AH can result in two clinical outcomes. While few studies show the mutations like V279F, R92H, A379V, D166E to be offering a favourable cardiovascular protective role.[51–57] Few other studies show V279F, R92H, A379V, D166E to be having a frank cardiovascular disease (CVD) risk.[54,58-65]

sPLA$_2$ Mutations and Benign Fleck Retina

GV sPLA$_2$ enzyme is located at the short arm of the chromosome 1 between p36 and p34; in humans it is expressed in the eyes and has the ability to hydrolyze glycerophospholipids, releasing bioactive lipids and free fatty acids.[66,67] This lipofuscin-like aggregates which is primarily composed of cross-linked lipid and protein at the retinal pigment epithelium (RPE) layer that gives rise to the focal thickening is referred to as 'fleck'.[68] Lipofuscin is a marker of membrane, mitochondria and lysosomes damage.[68,69]

Table 1 Human $sPLA_2$ Mutations and Their Clinical Implications

No.	Family	Mutations	Outcome of Mutations	Clinical Implications	Type of Study	Reference
1	GIID	G80S	Contributed to weight loss	Causes weight loss in patients with COPD	SNP study in 276 patients with COPD	83
2	GIID	G80S	Mutant cells showed increased levels of cytokines IL6 and IL8 as compared to the wild type	Associated with weight loss in patients with COPD	Culture cell experiments	78
3	GIID	G80S	Mutant cells showed increased levels of cytokines IL6 and IL8 as compared to the wild type	Associated with weight loss in patients with COPD	In silico analysis	34
4	GIIA	R123H	Affects substrate recognition and enzymatic activity	Adult respiratory distress syndrome	In silico analysis	95
5	GV	G45C	Decrease of phospholipase catalytic activity	Benign fleck retina	Homozygosity mapping and exome sequencing	67
6	GVII	V279F	Higher activity in stroke patients as compared to controls	Stroke	Genotyping studies	60
7	GVII	V279F	Lower Lp-PLA2 activity and Higher oxLDL level	Ischemic stroke	Genotyping and polymorphism studies	96
8	GVII	V279F	Enzyme activity was lower in heterozygote; complete lack of enzymatic activity in homozygotes	Not associated with coronary heart disease, myocardial infarction	Genotyping study and activity assay	46
9	GVII	V279F	Lower activity, Lower ox-LDL levels, lower HDL cholesterol level	Hypertension protected	Genotyping study and activity assay	51
10	GVII	V279F	Activity was 23–27% lower in heterozygote; no appreciable enzymatic activity in homozygote	Cardiovascular disease protected	Genotyping study and activity assay	53
11	GVII	D166E	Not available	Myocardial infarction	Genotyping study	65
12	GVII	V279F Q281R I317N	Decrease or complete loss of phospholipase catalytic activity	Hyperlipidemia and coronary heart disease	Transfection of COS-7 cultures with mutant constructs	66
13	GVII	V279F	Changes the protein profile, energy stability, and epitope shift; led to differences in their ability to induce IgG production in mice	Acute myocardial infarction	Immuno precipitation and immunization studies	97
14	GVII	V279F	Complete loss of Lp-PLA2 activity; high LDL cholesterol, increased lipid peroxidation and inflammation	Atherosclerosis	Genotyping studies and anthropometric studies	98

(*Continued*)

Table 1 (Continued).

No.	Family	Mutations	Outcome of Mutations	Clinical Implications	Type of Study	Reference
15	GVII	Q281R	Hypothesized to disrupt catalytic triad leading to loss of enzyme activity	Coronary artery disease, essential hypertension cardiomyopathy	Genotyping studies and enzyme activity assay	99
16	GVII	V279F	Loss of enzyme activity	Coronary artery disease/MI	Genotyping studies and enzyme activity assay	66,100
17	GVII	V279F	Activity was 50% lower in heterozygotes; no enzymatic activity in homozygote	Atherosclerotic occlusive disease	Genotyping study, activity assay	101
18	GVII	V279F	–	Coronary artery disease	Genotyping studies	102
19	GVII	V279F	Enzyme activity was lower in heterozygote, and further reduced in homozygote	Atherosclerosis	Genotyping study and activity assay	61
20	GVII	I198T	Reduced enzyme catalytic activity	Not associated with coronary heart disease (CHD), myocardial infarction (MI)	Genotyping study and activity assay	46
21	GVII	V279F	Activity was lower in heterozygote; no significant enzymatic activity in homozygote	Nonfamilial dilated cardiomyopathy	Genotyping study and activity assay	103
22	GVII	V279F	Mean plasma activity was significantly lower in heterozygotealong with low PAF acetylhydrolase levels, accumulation of PAF	Renal damage, hemolytic uremic syndrome	Genotyping study and activity assay	104
23	GVII	V279F	Enzyme activity is significantly reduced	Intravenous immunoglobulin nonresponse in patients with acute Kawasaki Disease	Genotyping study and activity assay	105
24	GVII	Q281R	Enzyme activity is significantly reduced	Asthma	Genotyping study and activity assay	106

Usually lipofuscin is regarded as aggregates of undigested cell materials that accumulates over a lifetime, occupying major portions of the RPE cell in elderly individuals and is a hallmark of aging.[69–72] Benign familial fleck retina (BFFR) is a congenital abnormality characterized by multi-focal small, round, distinctive diffuse yellow-white fleck-like lesions of varying size involving the postequatorial retina without the involvement of the central macula.[73] It is asymptomatic ocular condition with normal visual acuities in both eyes and the anterior segments of both eyes remains normal.[73] This trait is genetically inherited as an autosomal recessive disease related to a G45C mutation in GV $sPLA_2$.[66,68] GV $sPLA_2$ is known to contain 12 cysteines that form six disulfide bonds to stabilize its 3D structure.[74] It is not clear as to how the mutation affects the structure–function of the enzyme. However, with another cysteine in 46th position on a flexible loop, it is likely that a wrong disulfide bond is formed that affects its conformation while folding, thereby leading to a loss of function.

$sPLA_2$ Mutations and Weight Loss in Patients with Chronic Obstructive Pulmonary Disease (COPD)

COPD is airway diseases characterized by impaired air-flow in the respiratory tract, chronic airway inflammation,

as well as symptoms such as coughing, dyspnea, and wheezing.[75] The disease is not just confined to problems of airflow obstruction, but also has a major impact on cardiac function and air exchange, thereby resulting in systemic manifestations such as cardiovascular dysfunction, anemia, gastroesophageal reflux, depression, anxiety, osteoporosis, and weight loss in patients.[76] The cachexia that occurs in COPD is a result of muscle wasting and adipose tissue depletion and is linked to the systemic inflammation.[77–83] It assumes clinical importance because it limits patient's physical performance, compromises their quality of life and is also related to disease prognosis.[84,85] The weight loss is related to elevated levels of pro-inflammatory mediators such as tumor necrosis factor and interleukins.[78] However, in patients with COPD, the extent of weight loss varied and there was a wide distribution of pro-inflammatory mediators in the serum.[79,83,86,87] The $sPLA_2$ GIID protein consists of 125 amino acids and is constitutively expressed in the immune tissues humans and is upregulated by systemic pro-inflammatory stimuli in certain tissue tissues including the lung, suggesting its functional role in the progression of the inflammatory process.[6,88] G80S is a missense mutation that lies on a loop that forms the interfacial binding surface (IBS). Our team has shown that the mutant enzyme adopts an open conformation which increases interfacial binding surface area, thereby binding more potently to the M-type receptor compared to the wild $sPLA_2$.[34] Hence G80S mutation on human $sPLA_2$ GIID leads to enhanced expression of the cytokines that are responsible for the weight loss.[34,78]

Others Diseases Caused by $sPLA_2$ Mutations

A159T mutation in $sPLA_2$GVI is the causative for the neurological condition exhibiting familial cortical myoclonic tremor with epilepsy (FCMTE), an autosomal dominant epileptic syndrome, characterized by adult onset cortical myoclonic tremors of the extremities, epileptic seizures.[89,90] I198T and V379A are two mutations on PAF-AH that decreases substrate affinity and thus increased PAF concentration causing prolonged B cell survival that consequently leading to higher IgE levels leading to atopy and asthma.[91–93] R92H mutation in PAF-AH enzyme is reported to contribute to ischemic stroke susceptibility in the eastern Chinese Han population studied.[94]

Conclusions

$sPLA_2$s are among the smallest enzymes which perform various vital physiological functions. Despite their small size, $sPLA_2$ enzymes are complex puzzles with respect to their structure–function relationships. Certain $sPLA_2$s are expressed in different body tissues and have regulated function and housekeeping properties. While their upregulation is responsible for various disease states including cancer, there are also mutations that cause pathologies leading to a number of clinical scenarios. This review pertains to a detailed understanding of these mutations; their role on the structure–function relationship of the enzyme and the plausible mechanisms that lead to disease is fascinating. This knowledge is useful to comprehensively understand the role of these enzymes in human disease, and lays the platform for the designing of appropriate therapeutics for patient care.

Disclosure

The authors report no conflicts of interest in this work.

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