Phospholipase A_1

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Phospholipase A_1 (PLA_1) is an enzyme that cleaves an ester bond at the *sn*-1 position of glycerophospholipids, producing a free fatty acid and a lysophospholipid.

Keywords: phospholipase A1 ; phospholipid metabolism ; lysophospholipid

1. Introduction

Phospholipase A_1 (PLA_1) is an enzyme that hydrolyzes an ester bond at the *sn*-1 position of glycerophospholipids (GPLs), usually producing a saturated or mono-unsaturated fatty acid and a 1-lyso-2-acyl-phospholipid (2-acyl-lysophospholipid, 2-acyl-LPL) (**Figure 1**). PLA_1 has not attracted as much attention as other mammalian acyl hydrolases, such as phospholipase A_2 (PLA_2), which hydrolyzes fatty acids, mainly unsaturated fatty acids, and acts as a first step in producing enzymes for bioactive lipids such as eicosanoids and platelet-activating factor (PAF) [1][2]. Some PLA_1s and PLA_2 target neutral lipids such as triacylglycerol (TAG) and diacylglycerol (DAG) in addition to GPLs (**Figure 1**).

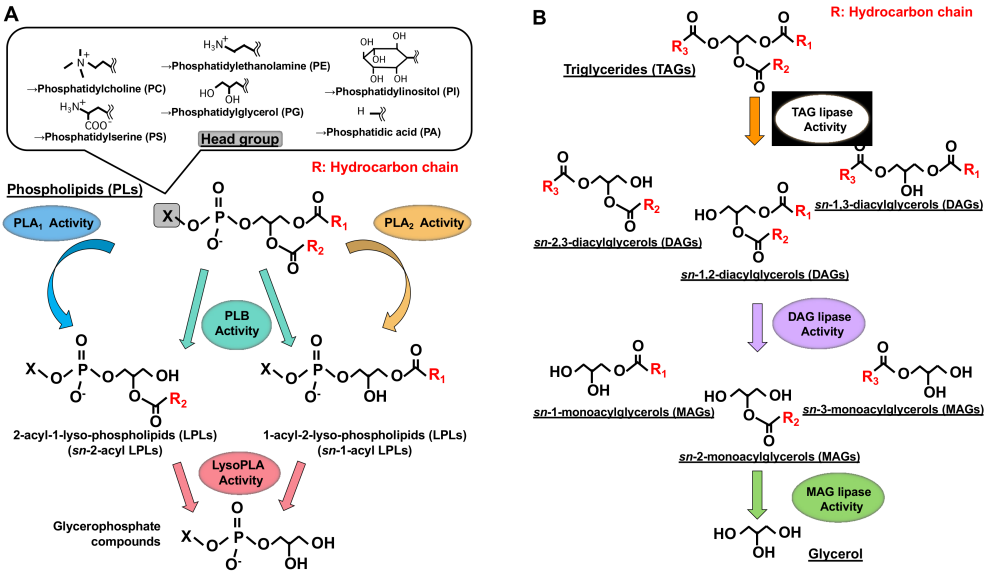

Figure 1. Structures of glycerolipids and their metabolic enzymes. (**A**) Glycerophospholipids (GPL) and phospholipases. GPLs are composed of a polar head group (six major classes), a glycerol backbone and fatty acid moieties (esterified at the *sn*-1 and *sn*-2 positions). Phospholipase A_1 (PLA_1) hydrolyzes a fatty acid at the *sn*-1 position, generating *sn*-2-acyl-1-lyso-phospholipids (*sn*-2-acyl LPLs), while phospholipase A_2 (PLA_2) hydrolyzes a fatty acid at the *sn*-2 position generating *sn*-1-acyl-2-lyso-phospholipids (*sn*-1-acyl LPLs). Phospholipase B (PLB) hydrolyzes a fatty acid at both *sn*-1 and *sn*-2 positions. LysoPLA hydrolyzes a fatty acid of *sn*-2-acyl LPLs and *sn*-1-acyl LPLs, generating glycerophosphate compounds. (**B**) Triacylglycerol (TAG) has three fatty acids at the *sn*-1, *sn*-2 and *sn*-3 positions of glycerol backbone, diacylglycerol (DAG) has two fatty acids and monoacylglycerol (MAG) has one fatty acid. TAG lipase hydrolyzes a fatty acid of TAG, generating *sn*-1, 2, *sn*-2, 3 or *sn*-1, 3-diacylglycerols (DAGs). DAG lipase hydrolyzes a fatty acid of DAG and MAG lipase hydrolyzes a fatty acid of MAG.

Much is known about the functions of PLA_2, whereas those of PLA_1 remain limited. However, because fatty acids at both the *sn*-1 and *sn*-2 positions of GPLs have a high turnover rate [3], PLA_1 as well as PLA_2, appears to be involved in the rapid turnover and remodeling of cellular GPLs (**Figure 2**). In addition, some PLA_1s also have a specific role in the production of 2-acyl-1-lysophospholipids, which serve as lysophospholipid mediators. For example, one type of PLA_1, membrane-associated phosphatidic acid-selective PLA_1 (mPA-$PLA_1\alpha$ in **Table 1**, **Figure 3**A), produces 2-acyl-1-lysophosphatidic acid (2-acyl-lysoPA (LPA)) with an unsaturated fatty acid residue [4]. The 2-acyl-LPA acts as a potent ligand for LPAR3/EDG7 and LPAR6/P2Y5, with LPA receptors preferring 2-acyl-LPA over 1-acyl-LPA [5][6].

Phosphatidylserine-specific PLA_1 (PS-PLA_1 in **Table 1**, **Figure 3**A) also acts as a producing enzyme of another lysophospholipid mediator, 2-acyl-lysophosphatidylserine (2-acyl-lysoPS (LysoPS)), which further supports the idea that PLA_1s function as producing enzymes for lysophospholipid mediators.

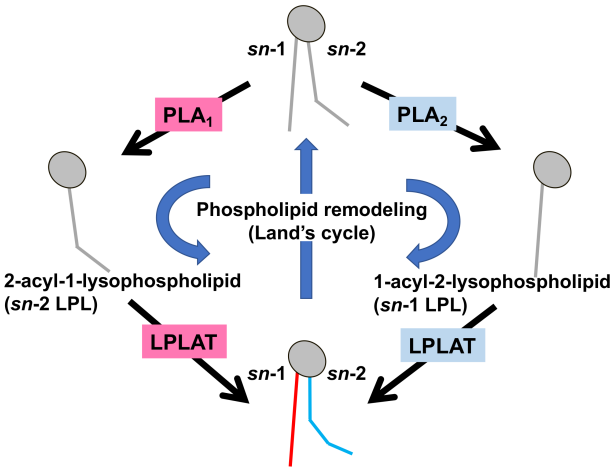

Figure 2. Fatty acid remodeling reactions of GPLs.

Glycerophospholipids (GPL) in the cells are constantly subjected to two kinds of fatty acid hydrolyzing reactions mediated by phospholipase A_1 (PLA_1) and phospholipase A_2 (PLA_2), resulting in the production of 2-acyl-1-lysophospholipid (*sn*-2 LPL) and 1-acyl-2-lysophospholipid (*sn*-1 LPL). The LPLs thus produced are further subjected to acylation reactions to re-form the GPLs. Several kinds of lysophospholipid acyltransferases (LPLAT) are responsible for the introduction of fatty acids to lysophospholipids. By these sequential GPL remodeling reactions, the fatty acids of GPLs are constantly replaced.

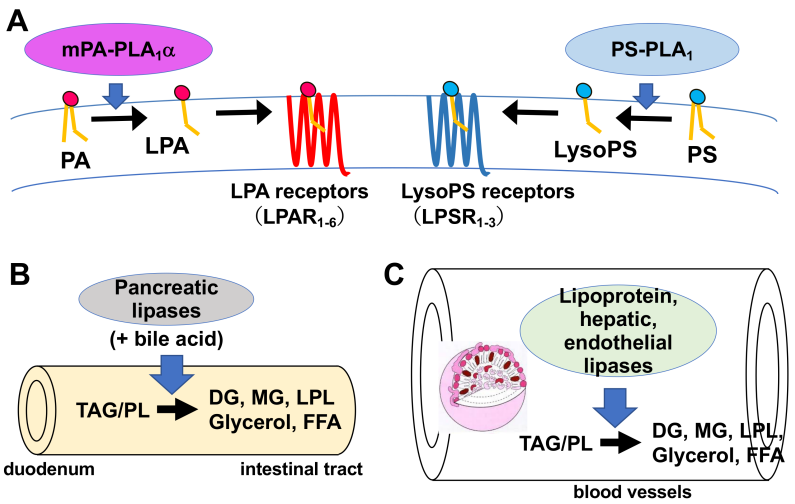

Figure 3. Physiological roles of extracellular PLA_1s. (**A**) PS-PLA_1 and mPA-PLA_1α serve as producing enzymes for lysophospholipid mediators. PS-PLA_1 has a strict substrate specificity in that it only acts on serine containing GPLs such as phosphatidylserine (PS) and lysophosphatidylserine (LysoPS). LysoPS then acts on GPCR-type LysoPS receptors. Three such LysoPS receptors have been identified. These include LPSR1/GPR34, LPSR2/P2Y10, and LPSR3/GPR174. mPA-PLA_1α acts on PA in a specific manner and produces *sn*-2 LPA, which then acts on GPCR-type LPA receptors, LPAR1-LPAR6 evoking various biological responses. (**B**) Pancreatic lipase (PL) is secreted from the pancreas into the lumen of the intestine, where it, with the aid of bile acids, hydrolyzes the fatty acids of triacylglycerol (TAG) and GPLs in the digestive juice yielding diacylglycerol (DAG), monoacylglycerol (MAG) and fatty acids. The liberated fatty acids are absorbed by intestinal cells as nutrients. (**C**) Lipoprotein lipase (LPL), hepatic lipase (HL), and endothelial lipase (EL), which are mainly present in the blood, are associated with endothelial cell surfaces in adipose tissues (LPL), heart (LPL), liver (HL) and various tissues. These lipases have both TAG lipase and PLA_1 activities. They hydrolyze fatty acids of TAG and GPLs present in the circulating lipoproteins such as low-density lipoproteins (LDL) and high-density lipoproteins (HDL), yielding diacylglycerol (DAG), monoacylglycerol (MAG), lysophospholipids (LPL) and fatty acids. The free fatty acids are absorbed by corresponding cells for energy source and storage of neutral lipids.

Table 1. Mammalian PLA_1s.

	Primary Name	Other Name	Human Gene	Substrate	Reaction Mediated	PDB ID (H: Human, R: Rat)	Ref.
extracellular PLA_1s	PS-PLA_1	PLA1A	*PLA1A*	PS	Producing enzyme for bioactive lysophospholipid, LysoPS	-	[7][8]
	PA-$PLA_1\alpha$	LIPH, mPA-$PLA_1\alpha$	*LIPH*	PA	Producing enzyme for bioactive lysophospholipid, LPA	-	[4][9]
	lipoprotein lipase	LPL, LIPD	*LIPD*	TAG, PL	TAG lipase and PLA_1 activity	H: 6E7K, 6OAU, 6OAZ, 6OB0, 6WN4	[10]
	hepatic lipase	HL, LIPC	*LIPC*	TAG, PL	TAG lipase and PLA_1 activity	-	[10]
	endothelial cell-derived lipase	EDL, EL, LIPG	*LIPG*	PL	Predominant PLA_1 activity	-	
	pacreatic lipase	PL, PNLIP	*PNLIP*	TAG, PL	TAG lipase and PLA_1 activity	H: 1GPL, 1LPA, 1LPB, 1N8S	[11] [12] [13]
	pancreatic lipase-related protein 1	PLRP1	*PLRP1*	TAG, PL	TAG lipase and PLA_1 activity	H: 2PPL	
	pancreatic lipase-related protein 2	PLRP2	*PLRP2*	TAG, PL	TAG lipase and PLA_1 activity	H: 2OXE, 2PVS; R: 1BU8	[11] [13]
	PA-PLA_1	DDHD1, $iPLA_1\alpha$	*DDHD1*	PL	PLA_1 activity	-	[14] [15]
	KIAA0725p	DDHD2, $iPLA_1\gamma$	*DDHD2*	PL	PE, DAG, CL	-	[16] [17] [18]
	p125	$iPLA_1\beta$	*P125*	n.d.	Enzymatic activity has not been detected	-	[19]
	PNPLA6	$iPLA_2\delta$, NTE	*PNPLA6*	PC, LPC	PLB, LysoPLA activity cleaving FAs at both *sn*-1 and *sn*-2 positions	-	[20] [21] [22]
	PNPLA7	$iPLA_2\theta$, NRE	*PNPLA7*	PC, LPC	PLB, LysoPLA activity cleaving FAs at both *sn*-1 and *sn*-2 positions	-	[23]
intracellular PLA_1s	PNPLA8	$iPLA_2\gamma$, Group VIB PLA_2	*PNPLA8*	PC	PLB activity cleaving FAs at both *sn*-1 and *sn*-2 positions	-	[24] [25]
	$cPLA_2\alpha$	PLA2G4A, Group IVA PLA_2	*PLA2G4A*	PL	PLB activity cleaving FAs at both *sn*-1 and *sn*-2 positions	H: 1BCI, 1CJY, 1RLW	[26]
	$cPLA_2\beta$	PLA2G4B, Group IVB PLA_2	*PLA2G4B*	PL	PLB activity cleaving FAs at both *sn*-1 and *sn*-2 positions	-	[26] [27]
	$cPLA_2\zeta$	PLA2G4F, Group IVF PLA_2	*PLA2G4F*	PL	PLB activity cleaving FAs at both *sn*-1 and *sn*-2 positions	-	
	PLA2G16	Group XVI PLA_2, PLAAT3, HRASLS3, H-Rev107	*PLA2G16*	PL	PLB activity cleaving FAs at both *sn*-1 and *sn*-2 positions	H: 2KYT, 4DOT, 4FA0, 4Q95, 7C3Z, 7C41	[28]

Although PLA_1 activity has been detected in many mammalian tissues and cells [29][30][31][32][33][34][35][36], only a few PLA_1s have been purified and cloned. Some triacylglycerol (TAG)-hydrolyzing lipases (**Figure 1**) such as hepatic lipase,

endothelial cell lipase, and lipoprotein lipase also show PLA_1 activity [11].

2. History of PLA_1 Research

The following is a brief history of mammalian PLA_1 research. PLA_1 as well as PLA_2 activities have been detected in various tissues and plasma. In the 1990's, two PLA_1 molecules were biochemically purified and identified. These two PLA_1s are phosphatidic acid-preferential PLA_1 (PA-PLA_1) and phosphatidylserine-specific PLA_1 (PS-PLA_1) (**Table 1**). In 1994, Higgs and Glomset purified a novel PLA_1 from a cytosolic fraction of bovine testes that preferentially hydrolyzed PA [14] (**Table 1**). Shortly after, the same group cloned a cDNA of the PLA_1, and PA-PLA_1 was found to be an intracellular protein composed of 875-amino acids with a calculated molecular mass of approximately 100 kDa. Simultaneously, Exton's group purified a very similar PLA_1 from the bovine brain [37]. It was not clear whether the two intracellular PLA_1s were identical, because the two groups used different PLA_1 assay conditions and substrates. Later, Kudo's group purified similar PLA_1s from the brain and testes of mice, rats, and cows [38] and showed that they were identical to the PA-PLA_1 mentioned above. They demonstrated that PA-PLA_1 was predominantly hydrolyzed phosphatidic acid (PA) in the presence of Triton X-100 and phosphatidylethanolamine (PE) in its absence. The result showed clearly that the substrate specificity of PA-PLA_1 in vitro is affected by the assay conditions, which makes it difficult to identify the natural substrates of PA-PLA_1. This also implies that the name, PA-PLA_1, is not suitable for the enzyme.

Horigome et al., detected two PLA activities in the supernatant of activated rat platelets [39][40]. One was identified as secretory PLA_2, now known as Group IIA secretory phospholipase A_2 (sPLA$_2$IIA). Sato et al., succeeded in purifying and cloning another PLA that showed a high preference for serine-containing phospholipids [7]. The PLA is now known as PS-specific PLA_1 (PS-PLA_1) (**Table 1**). PS-PLA_1 specifically hydrolyzed PS in vitro. In addition, it acted on the intact cell membrane, hydrolyzed PS and produced 2-acyl-LysoPS. Thus, PS-PLA_1 is believed to be a LysoPS-producing enzyme.

After discovering the two PLA_1 molecules, several researchers found similar PLA_1s (homologs) in the nucleotide databases, expressed them as recombinant proteins and characterized them biochemically. These analyses identified the homologs as novel PLA_1s. These include extracellular enzyme membrane-associated PA-selective PLA_1α (mPA-PLA_1α, a PS-PLA_1 homologue) [4] (**Table 1**) and intracellular enzyme iPLA$_1$γ/DDHD2/KIAA0725 (a PA-PLA_1 homologue) [16] and iPLA$_1$β/SEC23IP/p125 (PLA_1 activities have not been detected) [19] (**Table 1**). In addition, similar biochemical characterization was performed for PLA_2 homologs. Interestingly, biochemical characterizations of the PLA_2 homologs showed that some of them exhibited PLA_1 activity in addition to their PLA_2 activity (PLB activity (**Figure 1**)) (**Table 1**). It should also be noted here that certain lipases that hydrolyze TAG have PLA_1 activity, as mentioned above (**Table 1**). Lipases hydrolyze fatty acids at the *sn*-1 and *sn*-3 positions of triacylglycerol (TAG) and diacylglycerol (DAG). They also hydrolyze fatty acids at the *sn*-1 or *sn*-3 positions of monoacylglycerol (MAG). This research will summarize current knowledge on PLA_1 molecules reported thus far, discussing their discoveries, structures, tissue and cellular distributions, and possible biological functions.

PLA_1s are roughly divided into two groups: (1) extracellular PLA_1/lipase family and (2) intracellular PLA_1 family (**Table 1**), depending on their cellular localization and primary amino acid sequences. The intracellular PLA_1 family was further subdivided into several groups, consisting of an iPLA$_1$ family, PNPLA family, cPLA$_2$ family and PLAAT family.

3. Structural Evaluation of PLA_1 Molecules

Recently, a computational machine learning method named AlphaFold was developed enabling researchers to predict protein structures with high accuracy, even when no similar experimentally solved structure is available [41]. In this research, researchers utilized AlphaFold to generate structural predictions of PLA_1 molecules. **Figure 4** summarizes the AlphaFold-generated structures of some PLA_1 molecules focused on in this research. Note that some structures have been determined, e.g., by X-ray crystallography, while others were structure-predicted. Since structures of any PNPLA and iPLA$_1$ family members have not been determined, AlphaFold was unable to predict their structures. Thus, predicted structures were shown only for extracellular PLA_1/lipase and for cPLA$_2$ family members (**Figure 4**).

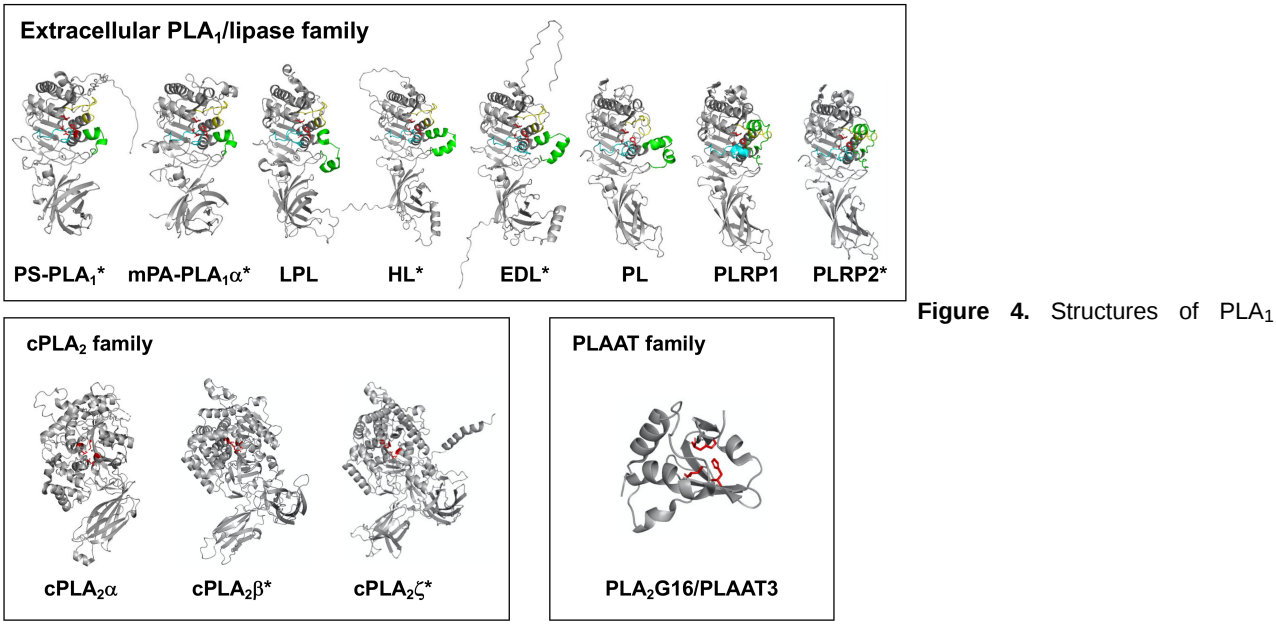

Figure 4. Structures of PLA_1 molecules. 3D structures of three PLA_1 family members (extracellular PLA_1/lipase, $cPLA_2$ and PLAAT family members) were shown. For extracellular PLA_1/lipase family members, β5 and the β9 loops and the lid domain are shown in yellow, cyan and green, respectively. The three residues forming a catalytic triad (Ser, Asp and His) are described as sticks (red). For $cPLA_2$ family members ($cPLA_2$α, $cPLA_2$β and $cPLA_2$ζ), the conserved lipase motifs (GXSGX and DXG) are shown in red, and the two residues forming a catalytic dyad (Ser and Asp) are shown as sticks. For PLAAT3/PLA2G16, the three residues forming a catalytic triad (two histidines and cysteine) are shown as sticks (red). The structures without asterisk were acquired from RCSB Protein Data Bank. (Reference PDB IDs; PL (1LPB), LPL (6OB0), PLRP1 (2PPL), $cPLA_2$α (1CJY), PLA2G16 (4DOT)). The predicted structures of lipases with asterisk were acquired from AlphaFold Protein Structure Database. All the structures were visualized using PyMOL software.

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