Review

Lipoquality control by phospholipase A₂ enzymes

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(Communicated by Kunihiro SUZUKI, M.J.A.)

Abstract: The phospholipase A₂ (PLA₂) family comprises a group of lipolytic enzymes that typically hydrolyze the *sn*-2 position of glycerophospholipids to give rise to fatty acids and lysophospholipids. The mammalian genome encodes more than 50 PLA₂s or related enzymes, which are classified into several subfamilies on the basis of their structures and functions. From a general viewpoint, the PLA₂ family has mainly been implicated in signal transduction, producing bioactive lipid mediators derived from fatty acids and lysophospholipids. Recent evidence indicates that PLA₂s also contribute to phospholipid remodeling for membrane homeostasis or energy production for fatty acid β -oxidation. Accordingly, PLA₂ enzymes can be regarded as one of the key regulators of the quality of lipids, which I herein refer to as *lipoquality*. Disturbance of PLA₂-regulated lipoquality hampers tissue and cellular homeostasis and can be linked to various diseases. Here I overview the current state of understanding of the classification, enzymatic properties, and physiological functions of the PLA₂ family.

Keywords: phospholipase, lipid, fatty acid, phospholipid, membrane, lipidomics

1. Introduction

In terms of signal transduction, the phospholipase A₂ (PLA₂) reaction, which hydrolyzes the *sn*-2 position of phospholipids to yield fatty acids and lysophospholipids, has been considered to be of particular importance, since arachidonic acid (AA, C20:4), one of the polyunsaturated fatty acids (PUFAs) released from membrane phospholipids by PLA₂, is metabolized by cyclooxygenases (COXs) and lipoxygenases (LOXs) to lipid mediators including prostaglandins (PGs) and leukotrienes (LTs), which are often referred to as eicosanoids (Fig. 1).

Lysophospholipids or their metabolites, such as lysophosphatidic acid (LPA) and platelet-activating factor (PAF), are categorized into another class of PLA₂-driven lipid mediators (Fig. 2A, B). More recently, a novel class of anti-inflammatory lipid mediators derived from ω 3 PUFAs, such as eicosapentaenoic acid (EPA, C20:5) and docosahexaenoic acid (DHA, C22:6), has also been attracting much attention (Fig. 2C). These lipid mediators exert numerous biological actions on target cells mainly by acting on their cognate G protein-coupled receptors. The pathophysiological roles of individual lipid mediators have been summarized in recent reviews.^{1)–4)}

However, this principal concept appears to be insufficient to fully explain the biological aspects and physiological roles of the PLA₂ family. Phospholipids comprise numerous molecular species that contain various combinations of fatty acids esterified at the *sn*-1 and *sn*-2 positions and several polar head groups at the *sn*-3 position. Many, if not all, PLA₂ enzymes recognize such differences in the fatty acyl and/or head group moieties in their substrate phospholipids. Moreover, several enzymes in the PLA₂ family also catalyze the phospholipase A₁ (PLA₁), lysophospholipase, neutral lipid lipase, or even transacylase/

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Fig. 1. The eicosanoid-biosynthetic pathway (AA metabolism). The AA released by PLA₂ from cellular membrane is metabolized to various eicosanoids through the COX and LOX pathways. Structures and representative bioactivities of individual eicosanoids and their biosynthetic enzymes are shown. H- and L-PGDS, hematopoietic and lipocalin-type PGD₂ synthases, respectively; PGFS, PGF_{2α} synthase; PGIS, PGI₂ synthase; mPGES-1, microsomal PGE₂ synthase-1; TXS, TX synthase; 12-HHT, 12-hydroxyheptadecatrienoic acid; 12-HETE, 12-hydroxyeicosatetraenoic acid; FLAP, 5-LOX-activating protein; LTA₄H, LTA₄ hydrolase; LTC₄S, LTC₄ synthase.

acyltransferase reaction rather than or in addition to the genuine PLA₂ reaction. Therefore, the fatty acids and lysophospholipids released by different PLA₂s are not always identical; rather, in many situations, specific fatty acids and lysophospholipids can be released by a particular PLA₂ in the presence of a given microenvironmental cue. In this context, PLA₂ enzymes act as one of the critical regulators of spatiotemporal lipid profiles, namely the quality of lipids (*lipoquality*). To comprehensively understand the lipoquality regulation by individual PLA₂s in various pathophysiological contexts, their precise enzymatic, biochemical and cell biological properties, tissue and cellular distributions, and availability of phospholipid substrates in various pathophysiological settings should be taken into consideration.

Herein, I overview current understanding of the biological aspects of various PLA₂ enzymes in the context of lipoquality.

2. Substrate specificity of PLA₂s; a general view

Obviously, the substrate specificity of individual PLA₂s is the critical determinant of lipoquality. The *in vitro* enzymatic activity of PLA₂s may be influenced by the assay conditions employed, such as the composition of the substrate phospholipids, concentrations of PLA₂s and substrates, presence of detergents, and pH. Hence, the enzymatic properties of individual PLA₂s determined in different studies may not be entirely identical. Since natural membranes contain numerous phospholipid molecular species, the results obtained using artificial phospho-

Fig. 2. Lysophospholipid-derived lipid mediators (LPA and PAF) and PUFA-derived anti-inflammatory lipid mediators (lipoxin, resolvin and protectin). (A) Two biosynthetic pathways for LPA. LPA is produced by fatty acid deacylation of phosphatidic acid (PA) by PLA₂ (or PLA₁), or by removal of the polar head group of lysophosphatidylcholine (LPC), which is produced from PC by PLA₂ (or PLA₁), by a lysophospholipase D termed autotaxin (ATX). In most if not all *in vivo* situations, the ATX-dependent route is dominant for the production of LPA. DAG, diacylglycerol; DGK, diacylglycerol kinase; PLD, phospholipase D. (B) Biosynthesis and degradation of PAF. Alkyl-PC is converted by PLA₂ to alkyl-LPC (LysoPAF), which is then acetylated by LPC acyltransferase 2 (LPCAT2) to give rise to PAF. PAF is deacetylated to LysoPAF by PAFAH, a unique group of PLA₂s. LysoPAF is converted back to alkyl-PC by LPCAT3. (C) Anti-inflammatory PUFA metabolites derived from ω6 AA (lipoxin A₄; LXA₄), ω3 EPA (resolvin E1; RvE1), and ω3 DHA (RvD1 and protectin D1; PD1). The double bond characteristic of the ω3 and ω6 PUFAs is shadowed.

lipid vesicles comprising only one or a few phospholipid species may not always reflect the true enzymatic properties of a given PLA₂. Addition of an excess amount of recombinant or purified PLA₂ to an enzyme assay often results in hydrolysis of bulk phospholipids, which makes precise evaluation of its substrate specificity difficult. The results obtained using a commercially available PLA₂ assay kit, in which a synthetic, chromophoric phospholipid is used as a substrate, should be interpreted carefully, since some PLA₂s are unable to hydrolyze it efficiently. In this regard, mass spectrometric examination of the *in vitro* hydrolysis of natural membrane phospholipids extracted from the affected tissues or cells by PLA₂, particularly at a low (physiologically relevant) concentration of the enzyme, could provide a valuable clue to the *in vivo* substrates and products of this enzyme.⁵⁾⁻⁷⁾ The overall tendency in this *in vitro* assay using natural membranes is recapitulated in several *in vivo* systems, often with even more

selective patterns of hydrolysis that are relevant to the results of studies using PLA₂ knockout and/or transgenic mice (see below). Importantly, the mobilization of distinct lipids by PLA₂s *in vivo* relies not only on their intrinsic enzymatic properties, but also on tissue- or disease-specific contexts such as the lipid composition of target membranes, the spatiotemporal availability of downstream lipid-metabolizing enzymes, or the presence of cofactor(s) that can modulate the enzymatic function, which may account for why distinct PLA₂ enzymes even in the same subfamily exert specific functions with different lipid profiles in distinct settings.

Hereafter, I describe the current understanding of various PLA₂s in the context of lipoquality. The classification, distributions, properties and functions of individual PLA₂s, whose pathophysiological functions have currently been studied using their gene-manipulated mice, are summarized in Table 1.

Table 1. Properties of PLA2 subtypes and their biological roles

Family	Number of isozymes	Nomenclature	General names	Distributions	Enzymatic functions	Lipid mobilization	Phenotypic outcomes in knockout (KO) mice	References
cPLA ₂	6	PLA2G4A	cPLA ₂ α	Ubiquitous	AA-specific PLA ₂	Production of AA metabolites or PAF	Attenuations of airway inflammation (acute lung injury, bronchial asthma, and pulmonary fibrosis), cerebral infarction, neurodegeneration (Alzheimer's disease), experimental autoimmune encephalomyelitis, collagen-induced arthritis, metabolic syndrome (atherosclerosis, obesity, and hepatic steatosis), and intestinal cancer. Exacerbations of ulcerative colitis, spinal cord injury, stress-induced cardiac hypertrophy, hemorrhage, female infertility, and renal function.	14–24
		PNPLA1	iPLA ₂ ε	Epidermal keratinocytes	ω-Oacylceramide transacylase	Production of ω-Oacylceramide for skin barrier formation	Lethal ichthyosis	68
		PNPLA2	iPLA ₂ ζ/ATGL	Ubiquitous (Abundant in adipose tissue and skeletal muscle)	TG lipase	Hydrolysis of TG in lipid droplets for fatty acid β-oxidation	TG accumulation in multiple tissues, Defective lipolysis and altered energy metabolism, Cardiac dysfunction, Protection from cancer-associated cachexia by preventing fat loss	57, 58, 60
		PMPLA3	iPLA ₂ ε/Adiponurin	Ubiquitous (Abundant in liver and adipose tissue)	TG lipase retinyl-palmitate lipase	Hepatic TG remodeling for neutral lipid accumulation	Impaired phagocytosis of macrophages and resistance to atherosclerosis (macrophage-specific KO)	144
							Hyperglycemia due to impaired insulin secretion (β-cell-specific KO)	145
							Perturbed hepatic fatty acid metabolism and TG accumulation under ER stress	146, 147
		PNPLA6	iPLA ₂ δ/NTE	Ubiquitous	Lysophospholipase	Hydrolysis of LPC	Exacerbation of nonalcoholic fatty liver disease (loss-of-function mutation)	64
							Embryonic lethality due to placental defect	48
							Neurodegeneration (neuron-specific KO)	148
		PNPLA7	iPLA ₂ θ/NRE	Ubiquitous	Lysophospholipase	Hydrolysis of LPC	Aberrant hepatic metabolism (unpublished data)	
		PNPLA8	iPLA ₂ γ/PLA2G6B	Ubiquitous	PLA ₁ or PLA ₂	Membrane (cardiolipin?) remodeling	Skeletal muscular weakness, heart failure, and impaired adaptive thermogenesis due to mitochondrial dysfunction and reduced β-oxidation, Resistant to diet-induced metabolic syndrome, Neurodegeneration, Susceptibility to parasitic infection, Platelet dysfunction	46, 149–153
		PNPLA9	iPLA ₂ β/PLA2G6	Ubiquitous	PLA ₂	Membrane remodeling	Male infertility, Impaired glucose-induced insulin secretion, Neurodegeneration, Aged-related bone loss, Reduction of pancreatic β-cell apoptosis, migration and contraction of vascular cells, and tumorigenesis of ovarian and breast cancers	54, 55, 154–158
PAF-AH	4	PLA2G7	PAFAH/Lp-PLA ₂	Plasma	PAF acetylhydrolase, oxidized phospholipid-specific PLA ₂	Hydrolysis of extracellular PAF, Degradation of oxidized phospholipids in lipoproteins	Protection from atherosclerosis (human mutations)	78
		PAFAH2	PAFAH2/PLA2G7B	Liver, Kidney	PAF acetylhydrolase, oxidized phospholipid-specific PLA ₂	Degradation of oxidized phospholipids in cell membranes	Protection from oxidative stress-induced liver damage	74
		PAFAH1B2	PLA2G8A/PAFAH1	Ubiquitous	PAF acetylhydrolase	Hydrolysis of intracellular PAF	Male infertility due to impaired testicular spermatogenesis, Reduced Aβ production	73, 159, 160
		PAFAH1B3	PLA2G8B/PAFAH1	Ubiquitous	PAF acetylhydrolase	Hydrolysis of intracellular PAF	Enlargement of ganglionic eminences in <i>Pafah1b3</i> ^{-/-} mice	161
		PLA2G15	Lysosomal PLA ₂	Ubiquitous	PLA ₁ or PLA ₂	Lysosomal degradation of phospholipids	Aberrant accumulation of non-degraded surfactant phospholipids in lysosomes of alveolar macrophages (phospholipidosis), Impaired selection and maturation of iNKT cells, Impaired adaptive T cell immunity against mycobacterium	80–82
		PLA2G16	HRASLS3/H-rev 107/PLAAT3	Adipocytes	PLA ₁ or PLA ₂ , N-acyl PE acyltransferase	Production of eicosanoids? N-acyl-PE metabolism?	Resistance to diet-induced obesity and metabolic syndrome	84

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Family	Number of isoforms	Nomenclature	General names	Distributions	Enzymatic functions	Lipid mobilization	Phenotypic outcomes in knockout (KO) mice	References
ABHD	19	ABHD2	Ubiquitous	Ubiquitous	Hydratase	PC metabolism?	Increase of smooth muscle cell migration and intimal hyperplasia, Pulmonary emphysema in aged mice due to altered surfactant phospholipid metabolism	161, 162
		ABHD3	Ubiquitous	Ubiquitous	Medium-chain and oxidatively truncated phospholipid-selective PLA ₁ or PLA ₂	Hydrolysis of phospholipids with medium-chain fatty acids	Impaired hydrolysis of myristoyl-phospholipids	90
		ABHD4	Ubiquitous	Ubiquitous	N-acyl-phospholipid-selective PLA ₁ or PLA ₂	Hydrolysis of N-acyl-phospholipids	Impaired hydrolysis of N-acyl-LPE	91
		ABHD5	Ubiquitous	Ubiquitous	Catalytically inactive	Acting as a cofactor for PNPLA2-mediated lipolysis	Impaired hydrolysis of TC, Lethal ichthyosis	163, 164
		ABHD6	Ubiquitous	Ubiquitous	Lysophospholipase or monoacylglycerol lipase	Hydrolysis of lysophospholipids and 2-AG	Impaired hydrolysis of 2-AG for microglia migration, Enhanced adipose browning, Attenuated diet-induced obesity and metabolic syndrome	92, 93, 165
		ABHD12	Ubiquitous	Ubiquitous	LysPS lipase	Hydrolysis of LysoPS	Massive accumulation of LysoPS in brain leading to age-dependent increases in microglial activation, auditory and motor defects	96, 97
		ABHD16A	Ubiquitous	Ubiquitous	PS lipase	Hydrolysis of PS	Lower LysoPS content in the CNS, Reduced body size, Decreased cytokine production by peritoneal macrophages	96
		PLA2G1B	sPLA ₂ -IB	Pancreatic acinar cells	PLA ₂	Dietary and biliary phospholipid digestion	Resistance to diet-induced obesity, insulin resistance, and atherosclerosis	105, 106, 108
		PLA2G2A	sPLA ₂ -IIA	Small intestinal Paneth cells, Leukocytes, Platelets, Epithelial cells	PLA ₂	Degradation of bacterial membrane phospholipids, Hydrolysis of microparticle phospholipids to yield eicosanoids and lysophospholipids	Resistance to bacterial infection (transgenic mice) Resistance to arthritis	113, 114, 115, 126, 166
		PLA2G2D	sPLA ₂ -IID	Lymphoid DCs	PLA ₂	Preferential production of ω 3 PUFA-derived pro-resolving lipid mediators	Increased susceptibility to colorectal cancer (natural mutation) Exacerbation of contact hypersensitivity and psoriasis, Protection from skin cancer and viral infection	167, 7, 116, 117
sPLA ₂	11	PLA2G2E	sPLA ₂ -IIE	Hypertrophic adipocytes, Hair follicles	PLA ₂	Hydrolysis of PE and PS in lipoproteins	Protection from diet-induced obesity and hyperlipidemia Modest abnormalities in hair follicles	119, 118
		PLA2G2F	sPLA ₂ -IIF	Epidermal keratinocytes	PLA ₂	Production of lysophosphatidogen	Protection from psoriasis and skin cancer	6
		PLA2G5	sPLA ₂ -V	Hypertrophic adipocytes, Bronchial epithelial cells, Macrophages, Smooth muscle cells, Cardiac myocytes	PLA ₂	Hydrolysis of PC in LDL to yield OA Hydrolysis of lung surfactant Production of eicosanoids? Production of LPE or cys-LTs?	Exacerbation of diet-induced obesity and associated metabolic phenotypes Neonatal death due to a respiratory defect (transgenic mice) Resistance to LPS-induced airway injury Reduced Th2 response and asthma Defective phagocytosis of harmful materials leading to increased susceptibility to infection and arthritis Protection from atherosclerosis (hematopoietic cell-specific KO), aortic rupture, and myocardial infarction	119, 123, 168, 124, 131, 125–127, 169–171
		PLA2G10	sPLA ₂ -X	Colorectal epithelial and goblet cells, Sperm	PLA ₂	Mobilization of ω 3 PUFAs Production of eicosanoids and LPC Hydrolysis of sperm membrane phospholipids to yield DPA and LPC Production of PGE ₂ ? Production of PUFAs that attenuate nuclear receptor signaling? Uncertain	Exacerbation of colitis and colorectal cancer Attenuation of asthma and influenza-induced pneumonia Reduced male fertility Reduced insulin secretion Hypocortisolemia, Reduced TLR4 signaling	24, 167, 130–132, 24, 129, 172, 173
		PLA2G3	sPLA ₂ -III	Epidermal epithelial cells, Mast cells	PLA ₂	Sperm membrane phospholipid remodeling	Impaired epididymal sperm maturation and male infertility	135
		PLA2G12B	sPLA ₂ -XIIIB	Hepatocytes	Catalytically inactive	Production of microenvironmental PGD ₂	Impaired mast cell maturation and associated anaphylaxis Steatohepatitis due to impaired hepatic VLDL secretion	136, 139
						Uncertain		

Enzymes whose *in vivo* functions have been analyzed using knockout mice are summarized.

3. Lipoquality control by intracellular PLA₂s

The cPLA₂ family. The cytosolic PLA₂ (cPLA₂) family comprises 6 isoforms (α – ζ), among which cPLA₂ β , δ , ε and ζ map to the same chromosomal locus (Fig. 3A).⁸ cPLA₂ α (also known as group IVA PLA₂) is undoubtedly the best known PLA₂ and its biological roles in association with lipoquality have been well documented.⁹ cPLA₂ α is the only PLA₂ that shows a striking substrate specificity for AA-containing phospholipids. Strictly speaking, cPLA₂ α can also hydrolyze phospholipids containing EPA, yet the low abundance of this ω 3 PUFA relative to other fatty acids including ω 6 AA in cell membranes allows cPLA₂ α to release AA rather specifically in most situations. Upon cell activation, cPLA₂ α translocates from the cytosol to the phosphatidylcholine (PC)-rich perinuclear,

endoplasmic reticulum (ER) and Golgi membranes (particularly Golgi) in response to an increase in the μ M range of cytosolic Ca²⁺ concentration, and is maximally activated by phosphorylation through mitogen-activated protein kinases (MAPKs) and other kinases.^{10,11} In addition, the phosphoinositide PIP₂ and ceramide-1-phosphate modulate the subcellular localization and activation of cPLA₂ α .^{12,13} The AA released by cPLA₂ α is converted by the sequential action of constitutive COX-1 or inducible COX-2 and terminal PG synthases to PGs or by the sequential action of 5-LOX and terminal LT synthases to LTs (Fig. 3B).

Mice deficient in cPLA₂ α display a number of phenotypes that can be explained by reductions of PGs and/or LTs. Under physiological conditions, cPLA₂ α -deficient mice display a hemorrhagic tendency, impaired female reproduction, gastrointestinal ulcer, and renal malfunction, among others.^{14–18} Under pathological conditions, cPLA₂ α -deficient mice are protected against bronchial asthma, pulmonary fibrosis, cerebral infarction, Alzheimer's disease, experimental autoimmune encephalomyelitis, collagen-induced arthritis, metabolic diseases, intestinal cancer and so on, whereas they suffer from more severe colitis and spinal cord injury.^{15,19–24} Most of these phenotypes are recapitulated in mice lacking one or more of the biosynthetic enzymes or receptors for PGs and LTs, lending strong support to the notion that cPLA₂ α lies upstream of eicosanoid biosynthesis in many situations. For instance, as is the case for cPLA₂ α -deficient mice, mice lacking LTC₄ synthase (LTC₄S), LTD₄ receptor (CysLT1), LTB₄ receptor (BLT1), or PGD₂ receptor (DP1) are protected from asthma,^{25–27} revealing the critical role of the cPLA₂ α -LTB₄/LTC₄/PGD₂ axis in this allergic disease. Likewise, the decrease of PGE₂ in cPLA₂ α -deficient mice can account largely, even if not solely, for the mitigation of arthritis, autoimmune encephalomyelitis, cancer and neurodegeneration as well as the exacerbation of colitis, since these phenotypes are mimicked by mice lacking PGE₂ synthase (mPGES-1) or either of the four PGE₂ receptors (EP1~4).^{28–32} Furthermore, cPLA₂ α -triggered release of AA by platelets is coupled not only with biosynthesis of the pro-thrombotic eicosanoid thromboxane A₂ (TXA₂), but also with β -oxidation-mediated bioenergetics for blood clotting.³³ Importantly, inherited human cPLA₂ α mutations are associated with reduced eicosanoid biosynthesis, platelet dysfunction, and intestinal ulceration,^{34,35} thus mimicking cPLA₂ α deletion in mice.

Fig. 3. The cPLA₂ family. (A) Structures of cPLA₂ enzymes (α – ζ). The C2 domain, which is essential for Ca²⁺-dependent membrane translocation, is conserved in cPLA₂ enzymes except for cPLA₂ γ , whose C-terminal region is farnesylated. (B) A schematic diagram of stimulus-induced cPLA₂ α activation. For details, see the text.

Fig. 4. The iPLA₂/PNPLA family. Structures of iPLA₂/PNPLA enzymes (PNPLA1~9), which are subdivided into lipase and phospholipase types, are shown. The patatin domain, which is characteristic of this family, is conserved in all of these enzymes. The biological functions and enzymatic properties of the individual enzymes are indicated on the right. For details, see the text.

On the other hand, the enzymatic activities and biological functions of cPLA₂ isoforms other than cPLA₂ α have remained largely unknown. Reportedly, cPLA₂ β (group IVB PLA₂), which has a unique JimC domain in the N-terminal region, display PLA₁, PLA₂ and lysophospholipase activities.³⁶⁾ cPLA₂ γ (group IVC PLA₂), which uniquely lacks the C2 domain characteristic of the cPLA₂ family, is C-terminally farnesylated and possesses lysophospholipase and transacylase activities in addition to PLA₂ activity.³⁷⁾ cPLA₂ δ (group IVD PLA₂), whose expression is elevated in human psoriatic skin,³⁸⁾ shows PLA₁ activity in preference to PLA₂ activity.³⁶⁾ cPLA₂ ϵ (group IVE PLA₂) exhibits a unique transacylase activity that transfers *sn*-1 fatty acid of PC to an amino residue of phosphatidylethanolamine (PE) to form *N*-acyl-PE, a precursor of the endocannabinoid lipid mediator *N*-acylethanolamine.³⁹⁾ cPLA₂ ζ (group IVF PLA₂) displays both PLA₁ and PLA₂ activities without fatty acid selectivity.⁴⁰⁾ However, these enzymatic properties of cPLA₂ β – ζ vary according to the *in vitro* assays employed, implying that analyses using gene-manipulated mice for these

enzymes will be necessary for clarifying their biological roles in the context of lipoquality.

The iPLA₂/PNPLA family. The human genome encodes 9 Ca²⁺-independent PLA₂ (iPLA₂) enzymes (Fig. 4). These enzymes are now more generally referred to as patatin-like phospholipase domain-containing lipases (PNPLA1~9), as all members in this family share a patatin domain, which was initially discovered in patatin (iPLA₂ α), a potato protein.^{41),42)} Mammalian iPLA₂/PNPLA isoforms include lipid hydrolases or transacylases with specificities for diverse lipids such as phospholipids, neutral lipids, sphingolipids, and retinol esters. Generally speaking, enzymes bearing a large and unique N-terminal region (PNPLA6~9) act mainly on phospholipids (phospholipase type), whereas those lacking the N-terminal domain (PNPLA1~5) act on neutral lipids (lipase type). Analysis of mutant mouse models and clinical symptoms of patients with mutations for these enzymes have provided valuable insights into the physiological roles of the iPLA₂/PNPLA family in various forms of homeostatic lipid metabolism that are fundamental for life.

Among the iPLA₂/PNPLA family, PNPLA9 (iPLA₂ β , also known as group VIA PLA₂) is the only isoform that acts primarily as a PLA₂ with poor fatty acid selectivity.^{43),44)} Although PNPLA8 (iPLA₂ γ or group VIB PLA₂) displays PLA₂ activity, it acts as a PLA₁ toward phospholipids bearing *sn*-2 PUFA.^{45),46)} Accordingly, hydrolysis of PUFA-bearing phospholipids by PNPLA8/iPLA₂ γ typically gives rise to 2-lysophospholipids (having a PUFA at the *sn*-2 position) rather than 1-lysophospholipids (having a saturated or monounsaturated fatty acid at the *sn*-1 position). PNPLA6 (iPLA₂ δ) and its closest paralog PNPLA7 (iPLA₂ θ) have lysophospholipase activity that cleaves lysophosphatidylcholine to yield fatty acid and glycerophosphocholine.^{47),48)} Genetic mutations or deletions of these phospholipid-targeting PNPLAs cause various forms of metabolic dysfunction and neurodegeneration.^{49)–53)} In particular, PNPLA9/iPLA₂ β is also referred to as the parkinsonism-associated protein PARK14, whose mutations impair Ca²⁺ signaling in dopaminergic neurons.⁵⁴⁾ Apart from the metabolic and neurodegenerative phenotypes, the lack of PNPLA9/iPLA₂ β leads to male infertility through an unknown mechanism.⁵⁵⁾

PNPLA2 (iPLA₂ ζ), more generally known as adipose triglyceride lipase (ATGL), is a major lipase that hydrolyzes triglycerides in lipid droplets to release fatty acids as a fuel for β -oxidation-coupled energy production, a process known as lipolysis.⁵⁶⁾ Genetic deletion or mutation of PNPLA2 leads to massive accumulation of triglycerides in multiple tissues leading to multi-organ failures,⁵⁷⁾ while protecting from cancer-associated cachexia by preventing fat loss.⁵⁸⁾ The activity of PNPLA2 is regulated positively by ABHD5 (see below) and negatively by perilipin and G0S2, which modulate the accessibility of PNPLA2 to lipid droplets.⁵⁹⁾ The fatty acids released from lipid droplets by PNPLA2 act as endogenous ligands for the nuclear receptor PPAR α or PPAR δ , which accelerates energy consumption.^{59),60)} The regulatory mechanisms and metabolic roles of PNPLA2 have been detailed in other elegant reviews.^{61),62)} Mutations of PNPLA3 (iPLA₂ ϵ) are highly associated with non-alcoholic fatty liver disease.⁶³⁾ Although the catalytic activity of PNPLA3 is controversial, it may serve as a triglyceride lipase, since its loss-of function mutation increases cellular triglyceride levels.⁶⁴⁾ Furthermore, recent evidence suggests that PNPLA3 acts as a retinyl-palmitate lipase in hepatic stellate cells to fine-tune the plasma levels of retinoids. The expressions of PNPLA2 and PNPLA3 are nutritionally regulated in a reciprocal

way; PNPLA2 is upregulated, while PNPLA3 is downregulated, upon starvation, and *vice versa* upon feeding.⁶⁵⁾ Biochemical and cell biological studies have suggested that PNPLA4 (iPLA₂ η , which is absent in mice) might be involved in retinol ester metabolism⁶⁶⁾ and that PNPLA5 might participate in triglyceride lipolysis coupled with autophagosome formation,⁶⁷⁾ although the *in vivo* relevance of these *in vitro* observations is unclear.

Unlike most PNPLA isoforms that are ubiquitously expressed in many tissues, PNPLA1 is localized predominantly in the upper layer of the epidermis. PNPLA1 acts as a unique transacylase, catalyzing the transfer of linoleic acid (LA; C18:2) in triglyceride to the ω -hydroxy residue of ultra-long-chain fatty acid in ceramide to form ω -*O*-acylceramide, a lipid component essential for skin barrier function.^{68),69)} Accordingly, genetic deletion or mutation of PNPLA1 hampers epidermal ω -*O*-acylceramide formation, thereby severely impairing skin barrier function and causing ichthyosis. The unique role of PNPLA1 in the acylceramide-metabolic pathway in the epidermis is depicted in Fig. 5.

The PAFAH family. The PAF-acetylhydrolase (PAFAH) family comprises one extracellular and three intracellular PLA₂s that were originally found to have the capacity to deacetylate and thereby inactivate the lysophospholipid-derived lipid mediator PAF.^{70),71)} Type-I PAFAH is a heterotrimer composed of two catalytic subunits, group XIII A and XIII B PLA₂s, and a regulatory subunit LIS-1, the causative gene for a type of Miller Diecker syndrome.⁷²⁾ Deficiency of type-I PAFAH leads to male infertility through an unknown mechanism.⁷³⁾ Type-II PAFAH (group VIIB PLA₂) preferentially hydrolyzes oxidized phospholipids (*i.e.*, phospholipids having an oxygenated fatty acid at the *sn*-2 position) in cellular membranes, thereby protecting cells from oxidative damage.⁷⁴⁾ Although plasma-type PAFAH (group VIIA PLA₂) is a secreted protein, it is described here as its structure is close to type-II PAFAH. Plasma-type PAFAH is now more generally called lipoprotein-associated PLA₂ (Lp-PLA₂), existing as a low-density lipoprotein (LDL)-bound form in human plasma.⁷⁵⁾ A series of studies have revealed the correlation of Lp-PLA₂ with atherosclerosis, likely because this enzyme liberates toxic oxidized fatty acids from modified LDL with pro-atherogenic potential.^{76),77)} Furthermore, deficiency of Lp-PLA₂ decreases intestinal polyposis and colon tumorigenesis in *Apc*^{Min/+} mice,⁷⁸⁾ suggesting an anti-tumorigenic role for PAF in this setting.

Fig. 5. The role of PNPLA1 in epidermal acylceramide biosynthesis. Structures of the metabolites and enzymes or transporters responsible for individual steps in the acylceramide-biosynthetic pathway are indicated. Mutations or deletions of these enzymes cause ichthyosis in both human and mouse. PNPLA1 catalyzes the transacylation of LA from triglyceride to ω -OH ceramide, leading to the formation of ω -O-acylceramide, which is an essential component of lipid lamellae and the cornified lipid envelope in the uppermost epidermis. For details, see the text. ELOVL6, fatty acid elongase 6; CYP4F22/39, cytochrome P450 family F22 (in human) and F39 (in mouse); CERS3, ceramide synthase 3; ABCA12, ABC transporter 12; UGCG, UDP-glucose ceramide glucosyltransferase; GBA, β -glucocerebrosidase; ALOXE3, epidermal-type lipoxygenase 3; ALOX12B, 12R-lipoxygenase; TGM1, transglutaminase 1.

Lysosomal PLA₂. Lysosomal PLA₂ (LPLA₂), also known as group XV PLA₂, is homologous with lecithin cholesterol acyltransferase (LCAT) and catalytically active under mildly acidic conditions.⁷⁹ LPLA₂ hydrolyzes both *sn*-1 and *sn*-2 fatty acids in phospholipids and contributes to phospholipid degradation in lysosomes. Genetic deletion of LPLA₂ results in unusual accumulation of non-degraded lung surfactant phospholipids in lysosomes of alveolar macrophages, leading to phospholipidosis,⁸⁰ perturbed presentation of endogenous lysophospholipid antigens to CD1d by invariant natural killer T (iNKT) cells,⁸¹ and impairment of adaptive T cell immunity against mycobacterium.⁸²

The PLAAT family. The PLA-acyltransferase (PLAAT) family (3 enzymes in humans and 5 enzymes in mice) is structurally similar to lecithin retinol acyltransferase (LRAT). Members of this family, including group XVI PLA₂ (PLA2G16),

display PLA₁ and PLA₂ activities, as well as acyltransferase activity that synthesizes *N*-acyl-PE, to various degrees.⁸³ PLA2G16 is highly expressed in adipocytes, and PLA2G16-deficient mice are resistant to diet-induced obesity.⁸⁴ PLA2G16 and its paralogs in this family have also been implicated in tumor invasion and metastasis,⁸⁵ vitamin A metabolism,⁸⁶ peroxisome biogenesis,⁸⁷ and cellular entry and clearance of Picornaviruses.⁸⁸

The ABHD family. The α/β hydrolase (ABHD) family is a newly recognized group of lipolytic enzymes, comprising at least 19 enzymes in humans.⁸⁹ Enzymes in this family typically possess both hydrolase and acyltransferase motifs. Although the functions of many of the ABHD isoforms still remain uncertain, some of them have been demonstrated to act on neutral lipids or phospholipids as lipid hydrolases. ABHD3 selectively hydrolyzes phospholipids with medium-chain fatty acids.⁹⁰

Fig. 6. The sPLA₂ family. The phylogenetic tree of sPLA₂ isoforms, which are subdivided into classical sPLA₂s (I/II/V/X branch) and atypical sPLA₂s (III and XII branches), is shown. The pathophysiological roles and related types of lipid metabolism (target substrates or products; shown in blue) for the individual isoforms are indicated. For details, see the text.

ABHD4 releases fatty acids from multiple classes of *N*-acyl-phospholipids to produce *N*-acyl-lysophospholipids.⁹¹⁾ ABHD6 acts as lysophospholipase or monoacylglycerol lipase, the latter being possibly related to the regulation of 2-arachidonoyl glycerol (2-AG) signaling.^{92),93)} 2-AG is an endocannabinoid lipid mediator that plays a role in the retrograde neurotransmission and is considered to be produced mainly by diacylglycerol lipase α .⁹⁴⁾ Interestingly, in the brain, the AA released from 2-AG by monoacylglycerol lipase, rather than that released from phospholipids by cPLA₂ α (see above), is linked to the production of a pool of PGE₂ that promotes fever.^{2),95)} ABHD12 hydrolyzes lysophosphatidylserine (LysoPS), and is therefore referred to as LysoPS lipase.⁹⁶⁾ Mutations in the human *ABHD12* gene result in accumulation of LysoPS in the brain and cause a disease called PHARC, which is characterized by polyneuropathy, hearing loss, ataxia, retinitis pigmentosa, and cataract.⁹⁷⁾ ABHD16A acts as a phosphatidylserine (PS)-selective PLA₂ (referred to as PS lipase), being located upstream of ABHD12 in the PS-catabolic pathway.⁹⁶⁾ Although ABHD5

(also called CGI-58) does not have a catalytic activity because of the absence of a serine residue in the catalytic center, it greatly enhances PNPLA2-directed hydrolysis of triglycerides in lipid droplets by acting as an essential lipolytic cofactor.⁹⁸⁾

4. Lipoquality control by secreted PLA₂s

General aspects. The secreted PLA₂ (sPLA₂) family contains 10 catalytically active isoforms and one inactive isoform in mammals.^{42),99)} Based on the structural and evolutionary relationships, these enzymes are categorized into classical (IB, IIA, IIC, IID, IIE, IIF, V and X) and atypical (III and XII) classes (Fig. 6). The sPLA₂ family strictly hydrolyzes the *sn*-2 position of phospholipids, a feature that differs from intracellular PLA₂s that often display PLA₁, lysophospholipase, lipase, or transacylase/acyltransferase activity (see above). Individual sPLA₂s exhibit unique tissue and cellular distributions, suggesting their distinct biological roles. As sPLA₂s are secreted and require Ca²⁺ in the mM range for their catalytic action, their principal targets are phospholipids in the extracellular space, such as microparticles,

surfactant, lipoproteins, and foreign phospholipids in microbe membranes or dietary components. The biochemical properties and pathophysiological functions of sPLA₂s have been detailed in several recent reviews.^{5),100)} Here, I describe several key features of lipoquality regulation by the sPLA₂ family.

In terms of the lipoquality, sPLA₂s have long been considered to display no apparent selectivity for *sn*-2 fatty acid species in the substrate phospholipids. This view was based on the fact that sPLA₂-IB and -IIA, two prototypic sPLA₂s that were initially identified through classical protein purification from the pancreas and sites of inflammation, respectively,^{101),102)} as well as a number of snake venom PLA₂s that belong to group I and II sPLA₂s, are capable of releasing fatty acids non-selectively. However, recent lipidomics-based evaluation of the substrate specificity of sPLA₂s toward natural membranes (see above) has revealed that several sPLA₂s can distinguish *sn*-2 fatty acyl moieties in phospholipids under physiologically relevant conditions. In general terms, sPLA₂-IB, -IIA and -IIE do not discriminate fatty acid species, sPLA₂-V tends to prefer those with a lower degree of unsaturation such as oleic acid (OA; C18:1), and sPLA₂-IID, -IIF, -III and -X tend to prefer PUFAs including AA and DHA. Several sPLA₂s can also distinguish differences in the polar head groups of phospholipids. For instance, sPLA₂-X is very active on PC, while sPLA₂-IIA has much higher affinity for PE than for PC, and this substrate selectivity has been partly ascribed to their crystal structures.^{103),104)} Therefore, in order to comprehensively understand the specific biological roles of this enzyme family, it is important to consider *when* and *where* different sPLA₂s are expressed, *which* isoforms are involved in *what* types of pathophysiology, *why* they are needed, and *how* they exhibit their unique functions by driving specific types of lipid metabolism.

Classical sPLA₂s. sPLA₂-IB, also known as “pancreatic sPLA₂”, is synthesized as an inactive zymogen in the pancreas, and its *N*-terminal propeptide is cleaved by trypsin to yield an active enzyme in the duodenum.¹⁰¹⁾ The main role of sPLA₂-IB is to digest dietary and biliary phospholipids in the intestinal lumen. Perturbation of this process by gene disruption or pharmacological inhibition of sPLA₂-IB leads to resistance to diet-induced obesity, insulin resistance, and atherosclerosis due to decreased phospholipid digestion and absorption in the gastrointestinal tract.^{105)–108)} The human *PLA2G1B* gene maps to an obesity-susceptible locus.¹⁰⁹⁾

sPLA₂-IIA is often referred to as “inflammatory sPLA₂”, since its expression is induced by pro-inflammatory cytokines such as TNF α and IL-1 β or by bacterial products such as lipopolysaccharide.¹¹⁰⁾ In mice, however, sPLA₂-IIA in mice is distributed only in intestinal Paneth cells (in BALB/c, C3H, NZB and DBA, *etc.*) or not expressed at all due to a natural frameshift mutation (in C57BL/6, A/J, C58/J, P/J, 129/Sv and B10.RIII, *etc.*).^{111),112)} The best-known physiological function of sPLA₂-IIA is the degradation of bacterial membranes, thereby providing the first line of antimicrobial defense in the host.^{113),114)} Consistent with this, sPLA₂-IIA preferentially hydrolyzes PE and phosphatidylglycerol, which are enriched in bacterial membranes. Under sterile conditions, sPLA₂-IIA attacks phospholipids in microparticles, particularly those in extracellular mitochondria (an organelle that evolutionally originated from bacteria), which are released from activated platelets or leukocytes at inflamed sites.¹¹⁵⁾ Hydrolysis of microparticulate phospholipids by sPLA₂-IIA results in production of pro-inflammatory eicosanoids and lysophospholipids as well as in release of mitochondrial DNA as a danger-associated molecular pattern (DAMP). Thus, sPLA₂-IIA is primarily involved in host defense by killing bacteria and triggering innate immunity, while over-amplification of the response leads to exacerbation of inflammation.

sPLA₂-IIA, -IIC, -IID, -IIE and -IIF are often classified into the group II subfamily (sPLA₂-IIC is a pseudogene in human), since they share structural characteristics and map to the same chromosome locus. sPLA₂-IID is constitutively expressed in dendritic cells (DCs) in lymphoid organs. sPLA₂-IID is an “immunosuppressive sPLA₂” that attenuates DC-mediated adaptive immunity by hydrolyzing PE probably in microparticles to mobilize anti-inflammatory ω 3 PUFAs and their metabolites such as resolvin D1 (RvD1).⁷⁾ As such, sPLA₂-IID-null mice exhibit more severe contact hypersensitivity and psoriasis, whereas they are protected against infection and cancer because of enhanced anti-viral and anti-tumor immunity.^{7),116),117)} Unlike sPLA₂-IIA, which is stimulus-inducible (see above), sPLA₂-IID is downregulated by pro-inflammatory stimuli, consistent with its anti-inflammatory role.

In mice, sPLA₂-IIE instead of sPLA₂-IIA is upregulated in several tissues under inflammatory or other conditions. sPLA₂-IIE is expressed in hair follicles in association with the growth phase of the hair cycle¹¹⁸⁾ and induced in adipose tissue in

Fig. 7. Properties of sPLA₂-IIF. (A) A schematic procedure for identification of the lipid metabolism driven by sPLA₂-IIF in differentiating keratinocytes. Phospholipids extracted from the culture supernatants of mouse keratinocytes (a representative mass spectrometric profile of phospholipids is shown; IS, internal standard; cps, count per second) were incubated with a physiologically relevant concentration of recombinant sPLA₂-IIF and then taken for the lipidomics analysis. (B) In the assay shown in (A), sPLA₂-IIF preferentially increased plasmalogen-type (P-) lysophosphatidylethanolamine (LPE) species as well as PUFAs. Values represent AUC (area under the curve; mean $\pm$ SEM, $n = 4$). (C) The results shown in (B), together with *in vivo* analyses using sPLA₂-IIF-transgenic and knockout mice,⁶⁾ indicate that sPLA₂-IIF preferentially hydrolyzes P-PE bearing DHA to liberate P-LPE and DHA under physiological conditions. For more details, please see ref. 6.

association with obesity in mice.¹¹⁹⁾ sPLA₂-IIE hydrolyzes PE without apparent fatty acid selectivity in hair follicles and lipoproteins, and accordingly, sPLA₂-IIE-deficient mice display subtle abnormalities in hair follicles¹¹⁸⁾ and are modestly protected from diet-induced obesity and hyperlipidemia.¹¹⁹⁾

sPLA₂-IIF has a long C-terminal extension containing a free cysteine, which might contribute to formation of a homodimer, and is more hydrophobic than other sPLA₂s.¹²⁰⁾ Physiologically,

sPLA₂-IIF is an “epidermal sPLA₂” that is expressed predominantly in the upper epidermis and induced by IL-22, a Th17 cytokine, in psoriatic skin.⁶⁾ sPLA₂-IIF preferentially hydrolyzes PUFA-containing plasmalogen-type PE in keratinocyte-secreted phospholipids to produce plasmalogen-type lysophosphatidylethanolamine (P-LPE; lysoplasmalogen), which in turn promotes epidermal hyperplasia (Fig. 7A–C). Accordingly, sPLA₂-IIF-null mice are protected against epidermal-hyperplastic diseases such as psor-

Fig. 8. Fatty acid selectivity of sPLA₂-V. Lipids extracted from the spleen of 1-year-old sPLA₂-V-deficient (-/-) and littermate control (+/+) mice were subjected to mass spectrometric lipidomics analysis (values are mean ± SEM, **P* < 0.05 and ***P* < 0.01). Experiments were performed in accordance with the procedure described previously (5). Y-axis indicate relative abundance (AUC; area under the curve) of each product per mg tissue. Free fatty acid (FFA) species with a lower degree of unsaturation, including PA (16:0), palmitoleic acid (16:1), stearic acid (18:0; SA), OA (18:1), LA (18:2), eicosanoic acid (20:0) and eicosenoic acid (C20:1), but not PUFAs including AA (20:4), EPA (20:5), DPA (22:5) and DHA (22:6), were significantly reduced in sPLA₂-V-deficient mice relative to control mice. Accordingly, LA metabolites, including 9- and 13-hydroxyoctadecadienoic acids (HODEs) among others, were substantially decreased in mutant mice relative to control mice, whereas none of the AA, EPA and DHA metabolites differed significantly between the genotypes. These results are consistent with the view that sPLA₂-V has a propensity to preferentially hydrolyze phospholipids having *sn*-2 fatty acids with a lower degree of unsaturation, as illustrated at right bottom.

iasis and skin cancer, while sPLA₂-IIF-transgenic mice spontaneously develop psoriasis-like skin.⁶⁾

Although sPLA₂-V was previously thought to be a regulator of AA metabolism,^{121),122)} it is now becoming obvious that this sPLA₂ has a preference for phospholipids having fatty acids with a lower degree of unsaturation. sPLA₂-V is markedly induced in adipocytes during obesity as a “metabolic sPLA₂” and hydrolyzes PC in hyperlipidemic LDL to release OA and to a lesser extent LA, which counteract adipose tissue inflammation and thereby ameliorates obesity-associated metabolic disorders.¹¹⁹⁾ Transgenic overexpression of sPLA₂-V, but not other sPLA₂s, results in neonatal death due to a respiratory defect,

which is attributable to the ability of sPLA₂-V to potentially hydrolyze PC with palmitic acid (PA, C16:0), a major component of lung surfactant.¹²³⁾ This unique substrate preference of sPLA₂-V has also been supported by a recent lipidomics analysis of the spleen (a tissue where sPLA₂-V is abundantly expressed), in which the levels of fatty acids with a lower degree of unsaturation (*e.g.* PA, OA and LA), rather than PUFAs (AA, EPA and DHA), are significantly reduced in sPLA₂-V-deficient mice relative to wild-type mice (Fig. 8). This is in contrast to the spleen of sPLA₂-IIF-deficient mice, in which ω3 PUFAs and their metabolites are selectively diminished,⁷⁾ revealing distinct lipoquality regulation

by different sPLA₂s. Another intriguing feature of sPLA₂-V is that it is the only “Th2-prone sPLA₂” induced in M2 macrophages by the Th2 cytokines IL-4 and IL-13 and promotes Th2-driven pathology such as asthma. Gene ablation of sPLA₂-V perturbs proper polarization and function of M2 macrophages in association with decreased Th2 immunity,¹²⁴ although the underlying lipid metabolism responsible for this event remains obscure. Probably because of this alteration in the macrophage phenotype, sPLA₂-V-null macrophages have a reduced ability to phagocytose extracellular materials. Accordingly, sPLA₂-V-null mice are more susceptible to fungal infection and arthritis due to defective clearance of hazardous fungi and immune complexes, respectively.^{125,126} Likewise, sPLA₂-V-null mice suffer from more severe lung inflammation caused by bacterial or viral infection,¹²⁷ which could also be explained by poor clearance of these microbes by alveolar macrophages.

Among the mammalian sPLA₂s, sPLA₂-X has the highest affinity for PC leading to release of fatty acids, with an apparent tendency for PUFA preference. sPLA₂-X is activated by cleavage of the N-terminal propeptide by furin-type convertases.¹²⁸ sPLA₂-X is expressed abundantly in colorectal epithelial and goblet cells and has a protective role in colitis by mobilizing anti-inflammatory ω 3 PUFAs.²⁴ Consistently, sPLA₂-X-transgenic mice exhibit global anti-inflammatory phenotypes in association with elevation of systemic ω 3 PUFA levels.²⁴ In the process of reproduction, sPLA₂-X secreted from the acrosomes of activated spermatozoa hydrolyzes sperm membrane phospholipids to release DHA and docosapentaenoic acid (DPA, C22:5), the latter facilitating fertilization.^{24,129} Additionally, sPLA₂-X-null mice are protected from asthma, accompanied by decreased levels of pulmonary ω 6 AA-derived eicosanoids.¹³⁰ Unlike the situation in sPLA₂-V-null mice (see above), however, the Th2 response *per se* is not affected in the asthma model¹³¹ and the lung damage is milder following influenza infection¹³² in sPLA₂-X-null mice, illustrating the distinct actions of different sPLA₂s in the same tissue.

Atypical sPLA₂s. sPLA₂-III is unusual in that it consists of three domains, in which the central sPLA₂ domain similar to bee venom group III sPLA₂ is flanked by large and unique N- and C-terminal domains.¹³³ The enzyme is processed to the sPLA₂ domain-only form that retains full enzymatic activity.¹³⁴ Although sPLA₂-III does not discriminate the polar head groups, it tends to prefer *sn*-2

PUFAs in the substrate phospholipids. sPLA₂-III is expressed in the epididymal epithelium and acts on immature sperm cells passing through the epididymal duct in a paracrine manner to allow sperm membrane phospholipid remodeling, a process that is prerequisite for sperm motility.¹³⁵ sPLA₂-III is also secreted from mast cells and acts on microenvironmental fibroblasts to produce PGD₂, which in turn promotes proper maturation of mast cells.¹³⁶ Accordingly, mice lacking sPLA₂-III exhibit male hypofertility and reduced anaphylactic responses.

sPLA₂-XIIA is evolutionally far distant from other sPLA₂s.¹³⁷ sPLA₂-XIIA is expressed in many tissues at relatively high levels, yet its enzymatic activity is weaker than that of other sPLA₂s. The properties and physiological roles of sPLA₂-XIIA are currently unclear and await future studies using sPLA₂-XIIA-deficient mice. Apart from lipoquality regulation, sPLA₂-XIIB is a catalytically inactive protein due to substitution of the catalytic center histidine by leucine.¹³⁸ sPLA₂-XIIB deficiency impairs hepatic lipoprotein secretion,¹³⁹ although the mechanism is unclear.

sPLA₂ receptor. Beyond the lipoquality control by sPLA₂s, several sPLA₂s binds to sPLA₂ receptor (PLA2R1, also known as the C-type lectin Clec13c) with different affinities.¹⁴⁰ In mice, PLA2R1 binds to sPLA₂-IB, -IIA, -IIE, -IIF and -X with high affinity, sPLA₂-V with moderate affinity, and sPLA₂-IID, -III and -XIIA with low or no affinity.¹³⁸ PLA2R1 is homologous to sPLA₂-inhibitory proteins present in snake plasma and exists as an integral membrane protein or as a soluble protein resulting from shedding or alternative splicing. PLA2R1 may act as a clearance receptor or endogenous inhibitor that inactivates sPLA₂s, as a signaling receptor that transduces sPLA₂-dependent signals in a catalytic activity-independent manner, or as a pleiotropic receptor that binds to non-sPLA₂ ligands. In support of its clearance role, *Pla2r1*^{-/-} mice show more severe asthma, likely due to defective clearance of pro-asthmatic sPLA₂-X.¹⁴¹ In support of its signaling role, PLA2R1, probably through binding to myocardial sPLA₂s or other ways, promotes the migration and growth of myofibroblasts and thereby protects against cardiac rupture in a model of myocardial infarction.¹⁴² PLA2R1 has recently attracted attention as a major autoantigen in membranous nephropathy, a severe autoimmune disease leading to podocyte injury and proteinuria,¹⁴³ although it is not clear whether this role of PLA2R1 is sPLA₂-dependent or -independent.

Table 2. Representative PLA₂ mutations in human diseases

Families	PLA ₂ genes	Human diseases	References
cPLA ₂	<i>PLA2G4A</i>	Platelet dysfunction, Intestinal ulceration	35
iPLA ₂	<i>PNPLA1</i>	Ichthyosis	177
	<i>PNPLA2</i>	Chanarin-Dorfman syndrome (neutral lipid storage disease with myopathy)	178
	<i>PNPLA3</i>	Non-alcoholic fatty liver disease (NAFLD)	63
		Ataxia, Hereditary spastic paraplegia, Boucher-Neuhauser and Gordon Holmes syndromes	179
	<i>PNPLA6</i>	Photoreceptor degeneration	53
	<i>PNPLA7</i>	Psychophysiological endophenotype	180
	<i>PNPLA8</i>	Myopathy	51
	<i>PNPLA9/PLA2G6</i>	Parkinson's disease, Infantile neuroaxonal dystrophy (INAD)	49
		Familial melanoma	181
PAFAH	<i>PAFAH/PLA2G7A</i>	Cardiovascular disease	182
ABHD	<i>ABHD5</i>	Chanarin-Dorfman Syndrome with ichthyosis	98
	<i>ABHD12</i>	PHARC syndrome (polyneuropathy, hearing loss, ataxia, retinitis pigmentosa, and cataract)	97
sPLA ₂	<i>PLA2G1B</i>	Obesity	109
	<i>PLA2G2A</i>	Cardiovascular disease	142, 183
		Gastric cancer	184
	<i>PLA2G2D</i>	Body weight loss in COPD (chronic obstructive pulmonary disease)	185
	<i>PLA2G2E</i>	Ulcerative colitis	186
		Colorectal cancer	187, 188
	<i>PLA2G3</i>	Alzheimer's disease	189
	<i>PLA2G5</i>	Hyperlipidemia in type II diabetes	114, 190
		Benign fleck retina	191

5. Concluding remarks

By applying lipidomics approaches to knockout or transgenic mice for various PLA₂s, it has become evident that individual enzymes regulate specific forms of lipid metabolism, perturbation of which can be eventually linked to distinct pathophysiological outcomes. Knowledge of lipoquality control by individual PLA₂s acquired from studies using animal models should be translated to humans. Current knowledges on the relationship between PLA₂ gene mutations and human diseases are summarized in Table 2. Nonetheless, future development of more comprehensive and highly sensitive lipidomics techniques will contribute to the discovery of novel PLA₂-driven lipid pathways that could be biomarkers or druggable targets for particular diseases.

Acknowledgments

I sincerely thank my laboratory members at the University of Tokyo and the Tokyo Metropolitan Institute of Medical Sciences who have contributed their expertise to acquire a better understanding of PLA₂ biology. In particular, I thank Drs. Kei Yamamoto, Tetsuya Hirabayashi, Yoshitaka Taketomi, Hiroyasu Sato, Yoshimi Miki, Remi Murase, Seiko Masuda and Noriko Ueno among others for collecting the experimental data and information on which this review is based. In the interest of brevity, I have referenced other reviews whenever possible and apologize to the authors of the numerous original papers that were not explicitly

cited. This work was supported by AMED-CREST from the Japan Agency for Medical Research and Development and by JSPS KAKENHI Grant Numbers JP15H05905 and JP16H02613.

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(Received May 9, 2017; accepted July 19, 2017)

Profile

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