Review

Lipoquality control by phospholipase A_2 enzymes

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Abstract: The phospholipase A_2 (PLA_2) 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 PLA_2s or related enzymes, which are classified into several subfamilies on the basis of their structures and functions. From a general viewpoint, the PLA_2 family has mainly been implicated in signal transduction, producing bioactive lipid mediators derived from fatty acids and lysophospholipids. Recent evidence indicates that PLA_2s also contribute to phospholipid remodeling for membrane homeostasis or energy production for fatty acid β-oxidation. Accordingly, PLA_2 enzymes can be regarded as one of the key regulators of the quality of lipids, which I herein refer to as *lipoquality*. Disturbance of PLA_2-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 PLA_2 family.

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

1. Introduction

In terms of signal transduction, the phospholipase A_2 (PLA_2) 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 PLA_2, 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 PLA_2-driven lipid mediators (Fig. 2A, B). More recently, a novel class of anti-inflammatory lipid mediators derived from ω3 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 PLA_2 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, PLA_2 enzymes recognize such differences in the fatty acyl and/or head group moieties in their substrate phospholipids. Moreover, several enzymes in the PLA_2 family also catalyze the phospholipase A_1 (PLA_1), lysophospholipase, neutral lipid lipase, or even transacylase/

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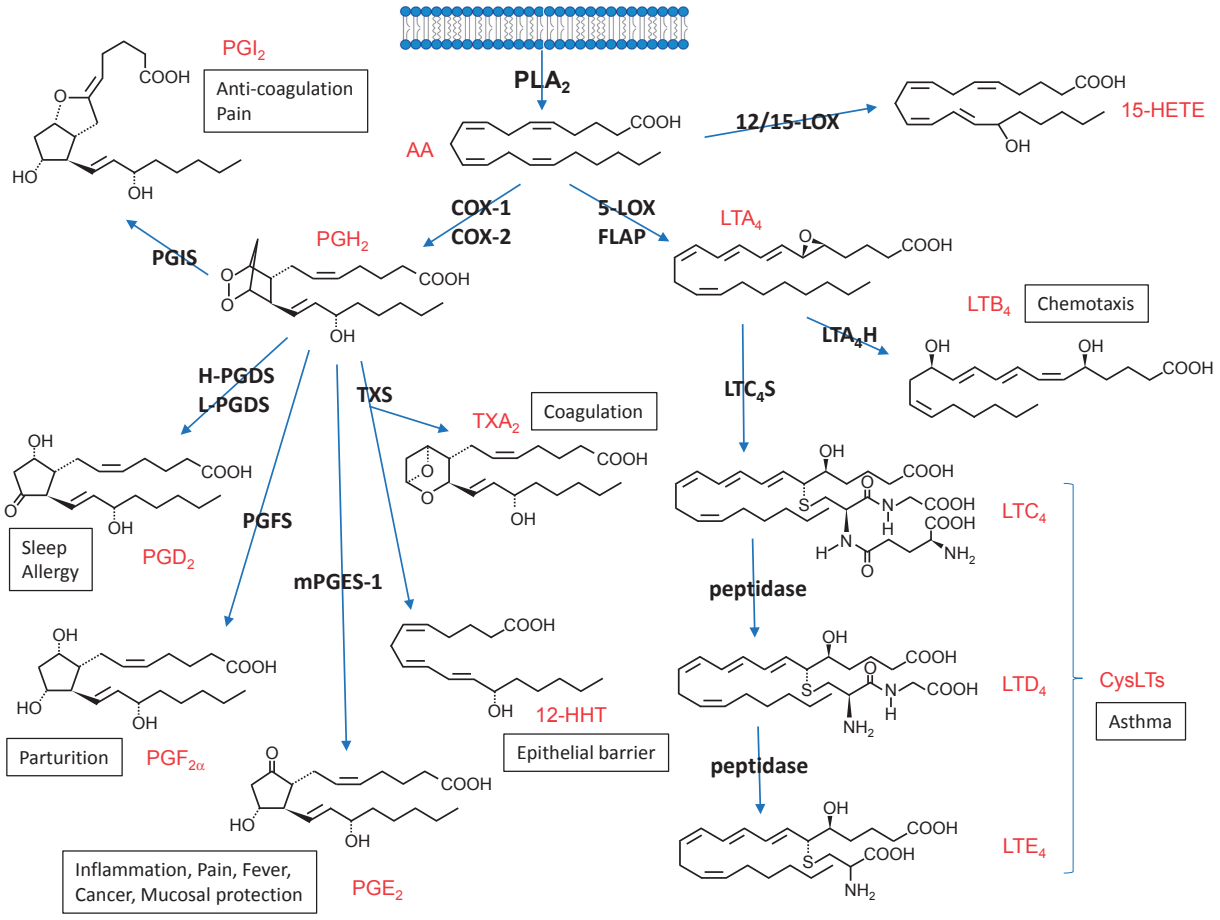

Fig. 1. The eicosanoid-biosynthetic pathway (AA metabolism). The AA released by PLA_2 from cellular membrane is metabolized to various eicosanoids through the COX and LOX pathways. Structures and representative bioactivities of individual eicosanoids and their biosynthetic enzymes are shown. H- and L-PGDS, hematopoietic and lipocalin-type PGD_2 synthases, respectively; PGFS, $PGF_{2\alpha}$ synthase, PGIS, PGI_2 synthase; mPGES-1, microsomal PGE_2 synthase-1; TXS, TX synthase; 12-HHT, 12-hydroxyheptadecatrenoic acid; 12-HETE, 12-hydroxyeicosatetraenoic acid; FLAP, 5-LOX-activating protein; LTA_4H, LTA_4 hydrolase; LTC_4S, LTC_4 synthase.

acyltransferase reaction rather than or in addition to the genuine PLA_2 reaction. Therefore, the fatty acids and lysophospholipids released by different PLA_2s are not always identical; rather, in many situations, specific fatty acids and lysophosholipids can be released by a particular PLA_2 in the presence of a given microenvironmental cue. In this context, PLA_2 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 PLA_2s 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 PLA_2 enzymes in the context of lipoquality.

2. Substrate specificity of PLA_2s; a general view

Obviously, the substrate specificity of individual PLA_2s is the critical determinant of lipoquality. The *in vitro* enzymatic activity of PLA_2s may be influenced by the assay conditions employed, such as the composition of the substrate phospholipids, concentrations of PLA_2s and substrates, presence of detergents, and pH. Hence, the enzymatic properties of individual PLA_2s determined in different studies may not be entirely identical. Since natural membranes contain numerous phospholipid molecular species, the results obtained using artificial phospho-

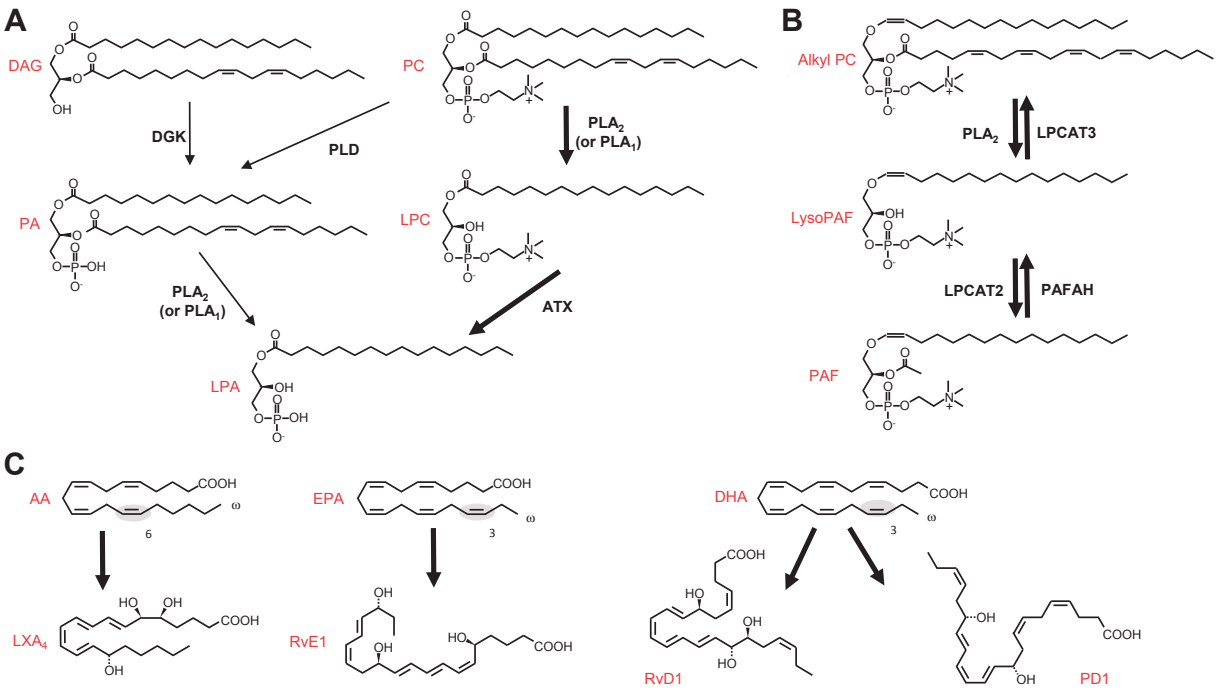

Fig. 2. Lysophospholipid-derived lipid mediators (LPA and PAF) and PUFA-derived anti-inflammatory lipid mediators (lipoxin, resolvin and protectin). (A) Two biosynthetic pathways for LPA. LPA is produced by fatty acid deacylation of phosphatidic acid (PA) by PLA_2 (or PLA_1), or by removal of the polar head group of lysophosphatidylcholine (LPC), which is produced from PC by PLA_2 (or PLA_1), 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 PLA_2 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 PLA_2s. LysoPAF is converted back to alkyl-PC by LPCAT3. (C) Anti-inflammatory PUFA metabolites derived from ω6 AA (lipoxin A_4; LXA_4), 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 PLA_2. Addition of an excess amount of recombinant or purified PLA_2 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 PLA_2 assay kit, in which a synthetic, chromophoric phospholipid is used as a substrate, should be interpreted carefully, since some PLA_2s 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 PLA_2, 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 PLA_2 knockout and/or transgenic mice (see below). Importantly, the mobilization of distinct lipids by PLA_2s *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 PLA_2 enzymes even in the same subfamily exert specific functions with different lipid profiles in distinct settings.

Hereafter, I describe the current understanding of various PLA_2s in the context of lipoquality. The classification, distributions, properties and functions of individual PLA_2s, 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	Phenotipic outcomes in knockout (KO) mice	References
cPLA$_2$	6	PLA2G4A	cPLA$_2\alpha$	Ubiquitous	AA-specific PLA$_2$	Production of AA metabolites or PAF	Attenuations of airway inflammation (acute lung injury, bronchial asthma, and plumonary 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
iPLA$_2$	9	PNPLA1		Epidermal keratinocytes	ω-*O*-acylceramide transacylase	Production of ω-*O*-acylceramide for skin barrier formation	Lethal ichthyosis	68
		PNPLA2	iPLA$_2\zeta$/ 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 alterd energy metabolism, Cardiac dysfunction, Protection from cancer-associated cachexia by preventing fat loss Impaired phagocytosis of macrophages and resistance to atherosclerosis (macrophage-specific KO) Hyperglycemia due to impaired insulin secretion (β-cell-specific KO)	57, 58, 60 144 145
		PMPLA3	iPLA$_2\varepsilon$/ Adiponutrin	Ubiquitous (Abundant in liver and adipose tissue)	TG lipase retinyl-palmitate lipase	Hepatic TG remodeling for neutral lipid accumulation	Perturbed hepatic fatty acid metabolism and TG accumulation under ER stress Exacerbation of nonalcoholic fatty liver disease (loss-of-function mutation)	146, 147 64
		PNPLA6	iPLA$_2\delta$/NTE	Ubiquitous	Lysophospholipase	Hydrolysis of LPC	Embryonic lethality due to placental defect Neurodegeneration (neuron-specific KO)	48 148
		PNPLA7	iPLA$_2\theta$/NRE	Ubiquitous	Lysophospholipase	Hydrolysis of LPC	Aberrant hepatic metabolism (unpublished data)	
		PNPLA8	iPLA$_2\gamma$/ PLA2G6B	Ubiquitous	PLA$_1$ or PLA$_2$	Membrane (caldiolipin?) remodeling Production of arachidonate metabolites or PUFA-containing lysophospholipids	Skeletal muscular weakness, heart failure, and impaired adaptive thermogenesis due to mitochondorial dysfunction and reduced β-oxidation, Resistant to diet-induced metabolic syndrome, Neurodegeneration, Susceptibility to parasitic infection, Platelet dysfunction	46, 149–153
		PNPLA9	iPLA$_2\beta$/ PLA2G6	Ubiquitous	PLA$_2$	Membrane remodeling Production of AA metabolites or PAF	Male infertility, Impaired glucose-induced insulin secreteion, 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) Resistance to colon tumorigenesis	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 α1 subunit	Ubiquitous	PAF acetylhydrolase	Hydrolysis of intracellular PAF	Male infertility due to impaired testicular spermatogenesis, Reduced Aβ production	73, 159, 160
		PAFAH1B3	PLA2G8B/ PAFAH1 α2 subunit	Ubiquitous	PAF acetylhydrolase	Hydrolysis of intracellular PAF	Enlargement of ganglionic eminences in *Pafah1b2*$^{-/-}$*Pafah1b3*$^{-/-}$ mice	161
LPLA2	1	PLA2G15	Lysosomal PLA$_2$	Ubiquitous	PLA$_1$ or PLA$_2$	Lysosomal degradation of phospholipids	Abberant 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
PLAAT	5	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 isozymes	Nomenclature	General names	Distributions	Enzymatic functions	Lipid mobilization	Phenotipic outcomes in knockout (KO) mice	References
ABHD	19	ABHD2		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	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	*N*-acyl-phospholipid-selective PLA_1 or PLA_2	Hydrolysis of *N*-acyl-phospholipids	Impaired hydrolysis of *N*-acyl-PE	91
		ABHD5	CGI-58	Ubiquitous	Catalytically inactive	Acting as a cofactor for PNPLA2-mediated lipolysis	Impaired hydrolysis of TG, Lethal ichthyosis	163, 164
		ABHD6		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	LysoPS 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	PS lipase	Hydrolysis of PS	Lower lysoPS content in the CNS, Reduced body size, Decreased cytokine production by peritoneal macrophages	96
$sPLA_2$	11	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 microparticular phospholipids to yield eicosanoids and lysophospholipids	Resistance to bacterial infection (transgenic mice) Resistance to arthritis Increased susceptibility to colorectal cancer (natural mutation)	113, 114 115, 126, 166 167
		PLA2G2D	$sPLA_2$-IID	Lymphoid DCs	PLA_2	Preferential production of ω3 PUFA-derived pro-resolving lipid mediators	Exacervation of contact hypersensitivity and psoriasis, Protection from skin cancer and viral infection	7, 116, 117
		PLA2G2E	$sPLA_2$-IIE	Hypertrophic adipocytes, Hair follicles	PLA_2	Hydrolysis of PE and PS in lipoproteins Uncertain	Protection from diet-induced obesity and hyperlipidemia Modest abnormalities in hair follicles	119 118
		PLA2G2F	$sPLA_2$-IIF	Epidermal keratinocytes	PLA_2	Production of lysoplasmalogen	Protection from psoriasis and skin cancer	6
		PLA2G5	$sPLA_2$-V	Hypertrophic adipocytes, Bronchial epithelial cells, Macrophages, Smooth muscle cells, Cardiomyocytes	PLA_2	Hydrolysis of PC in LDL to yield OA Hydrolysis of lung surfactant Production of eicosanoids? Production of LPE or cys-LTs? Uncertain	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 ω3 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 Hypercorticosteronemia, Reduced TLR4 signaling Exacerbation of atherosclerosis with increased Th1 immunity (hematopoietic cell-specific KO), Reduced nociception, Attenuation of aneurysm and myocardial infarction	24, 167 130–132 24, 129 172 173 174–176
		PLA2G3	$sPLA_2$-III	Epididymal epithelial cells, Mast cells	PLA_2	Sperm membrane phospholipid remodeling Production of microenvironmental PGD_2	Impaired epididymal sperm maturation and male infertility Impaired mast cell maturation and associated anaphylaxis	135 136
		PLA2G12B	$sPLA_2$-XIIB	Hepatocytes	Catalytically inactive	Uncertain	Steatohepatitis due to impaired hepatic VLDL secretion	139

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

3. Lipoquality control by intracellular PLA_2s

The $cPLA_2$ family. The cytosolic PLA_2 ($cPLA_2$) family comprises 6 isoforms (α–ζ), among which $cPLA_2\beta$, δ, ε and ζ map to the same chromosomal locus (Fig. 3A).[8] $cPLA_2\alpha$ (also known as group IVA PLA_2) is undoubtedly the best known PLA_2 and its biological roles in association with lipoquality have been well documented.[9] $cPLA_2\alpha$ is the only PLA_2 that shows a striking substrate specificity for AA-containing phospholipids. Strictly speaking, $cPLA_2\alpha$ can also hydrolyze phospholipids containing EPA, yet the low abundance of this ω3 PUFA relative to other fatty acids including ω6 AA in cell membranes allows $cPLA_2\alpha$ to release AA rather specifically in most situations. Upon cell activation, $cPLA_2\alpha$ 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 μM range of cytosolic Ca^{2+} concentration, and is maximally activated by phosphorylation through mitogen-activated protein kinases (MAPKs) and other kinases.[10),11] In addition, the phosphoinositide PIP_2 and ceramide-1-phosphate modulate the subcellular localization and activation of $cPLA_2\alpha$.[12),13] The AA released by $cPLA_2\alpha$ 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).

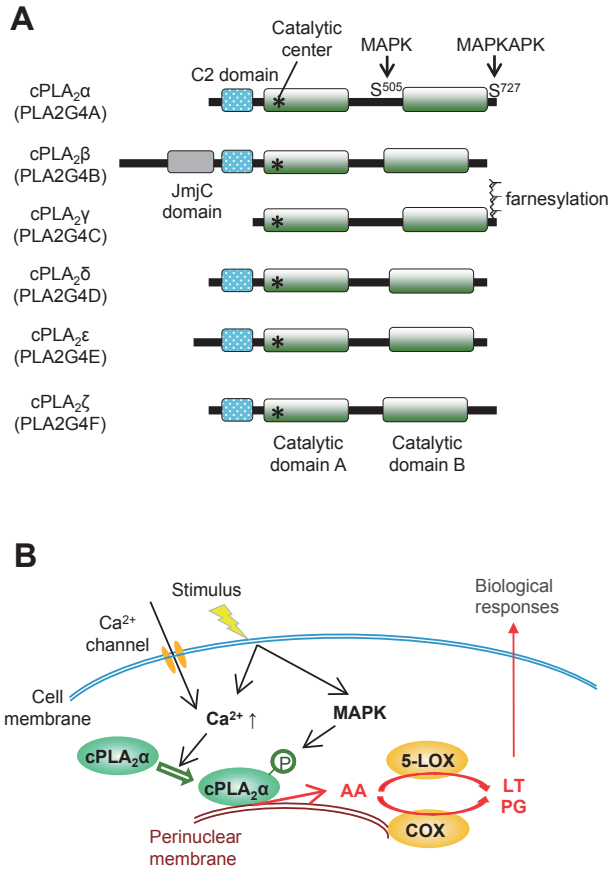

Fig. 3. The $cPLA_2$ family. (A) Structures of $cPLA_2$ enzymes (α-ζ). The C2 domain, which is essential for Ca^{2+}-dependent membrane translocation, is conserved in $cPLA_2$ enzymes except for $cPLA_2\gamma$, whose C-terminal region is farnesylated. (B) A schematic diagram of stimulus-induced $cPLA_2\alpha$ activation. For details, see the text.

Mice deficient in $cPLA_2\alpha$ display a number of phenotypes that can be explained by reductions of PGs and/or LTs. Under physiological conditions, $cPLA_2\alpha$-deficient mice display a hemorrhagic tendency, impaired female reproduction, gastrointestinal ulcer, and renal malfunction, among others.[14)–18] Under pathological conditions, $cPLA_2\alpha$-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 $cPLA_2\alpha$ lies upstream of eicosanoid biosynthesis in many situations. For instance, as is the case for $cPLA_2\alpha$-deficient mice, mice lacking LTC_4 synthase (LTC_4S), LTD_4 receptor (CysLT1), LTB_4 receptor (BLT1), or PGD_2 receptor (DP1) are protected from asthma,[25)–27] revealing the critical role of the $cPLA_2\alpha$-LTB_4/LTC_4/PGD_2 axis in this allergic disease. Likewise, the decrease of PGE_2 in $cPLA_2\alpha$-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 PGE_2 synthase (mPGES-1) or either of the four PGE_2 receptors (EP1∼4).[28)–32] Furthermore, $cPLA_2\alpha$-triggered release of AA by platelets is coupled not only with biosynthesis of the pro-thrombotic eicosanoid thromboxane A_2 (TXA_2), but also with β-oxidation-mediated bioenergetics for blood clotting.[33] Importantly, inherited human $cPLA_2\alpha$ mutations are associated with reduced eicosanoid biosynthesis, platelet dysfunction, and intestinal ulceration,[34),35] thus mimicking $cPLA_2\alpha$ deletion in mice.

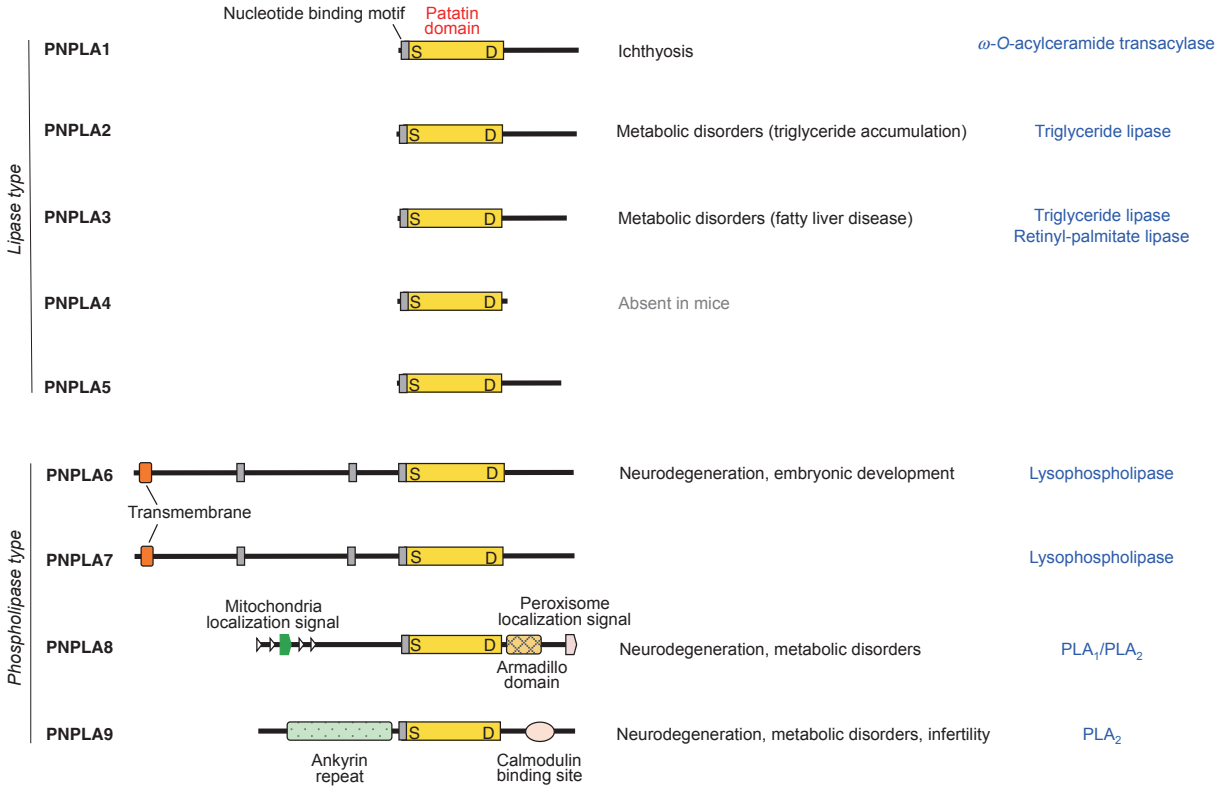

Fig. 4. The $iPLA_2$/PNPLA family. Structures of $iPLA_2$/PNPLA enzymes (PNPLA1∼9), which are subdivided into lipase and phospholipase types, are shown. The patatin domain, which is characteristic of this family, is conserved in all of these enzymes. The biological functions and enzymatic properties 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 $cPLA_2$ isoforms other than $cPLA_2\alpha$ have remained largely unknown. Reportedly, $cPLA_2\beta$ (group IVB PLA_2), which has a unique JimC domain in the N-terminal region, display PLA_1, PLA_2 and lysophospholipase activities.[36] $cPLA_2\gamma$ (group IVC PLA_2), which uniquely lacks the C2 domain characteristic of the $cPLA_2$ family, is C-terminally farnesylated and possesses lysophospholipase and transacylase activities in addition to PLA_2 activity.[37] $cPLA_2\delta$ (group IVD PLA_2), whose expression is elevated in human psoriatic skin,[38] shows PLA_1 activity in preference to PLA_2 activity.[36] $cPLA_2\varepsilon$ (group IVE PLA_2) 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] $cPLA_2\zeta$ (group IVF PLA_2) displays both PLA_1 and PLA_2 activities without fatty acid selectivity.[40] However, these enzymatic properties of $cPLA_2\beta$–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 $iPLA_2$/PNPLA family. The human genome encodes 9 Ca^{2+}-independent PLA_2 ($iPLA_2$) 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 ($iPLA_2\alpha$), a potato protein.[41,42] Mammalian $iPLA_2$/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 $iPLA_2$/PNPLA family in various forms of homeostatic lipid metabolism that are fundamental for life.

Among the iPLA$_2$/PNPLA family, PNPLA9 (iPLA$_2\beta$, also known as group VIA PLA$_2$) is the only isoform that acts primarily as a PLA$_2$ with poor fatty acid selectivity.[43),44)] Although PNPLA8 (iPLA$_2\gamma$ or group VIB PLA$_2$) displays PLA$_2$ activity, it acts as a PLA$_1$ toward phospholipids bearing *sn*-2 PUFA.[45),46)] Accordingly, hydrolysis of PUFA-bearing phospholipids by PNPLA8/iPLA$_2\gamma$ 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 (iPLA$_2\delta$) and its closest paralog PNPLA7 (iPLA$_2\theta$) 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/iPLA$_2\beta$ is also referred to as the parkinsonism-associated protein PARK14, whose mutations impair Ca^{2+} signaling in dopaminergic neurons.[54)] Apart from the metabolic and neurodegenerative phenotypes, the lack of PNPLA9/iPLA$_2\beta$ leads to male infertility through an unknown mechanism.[55)]

PNPLA2 (iPLA$_2\zeta$), 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 PPARα or PPARδ, 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 (iPLA$_2\varepsilon$) 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 (iPLA$_2\eta$, which is absent in mice) might be involved in retinol ester metabolism[66)] 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 PLA$_2$s 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 XIIIA and XIIIB PLA$_2$s, 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 PLA$_2$) 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 PLA$_2$) 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 PLA$_2$ (Lp-PLA$_2$), existing as a low-density lipoprotein (LDL)-bound form in human plasma.[75)] A series of studies have revealed the correlation of Lp-PLA$_2$ with atherosclerosis, likely because this enzyme liberates toxic oxidized fatty acids from modified LDL with pro-atherogenic potential.[76),77)] Furthermore, deficiency of Lp-PLA$_2$ decreases intestinal polyposis and colon tumorigenesis in $Apc^{Min/+}$ mice,[78)] suggesting an anti-tumorigenic role for PAF in this setting.

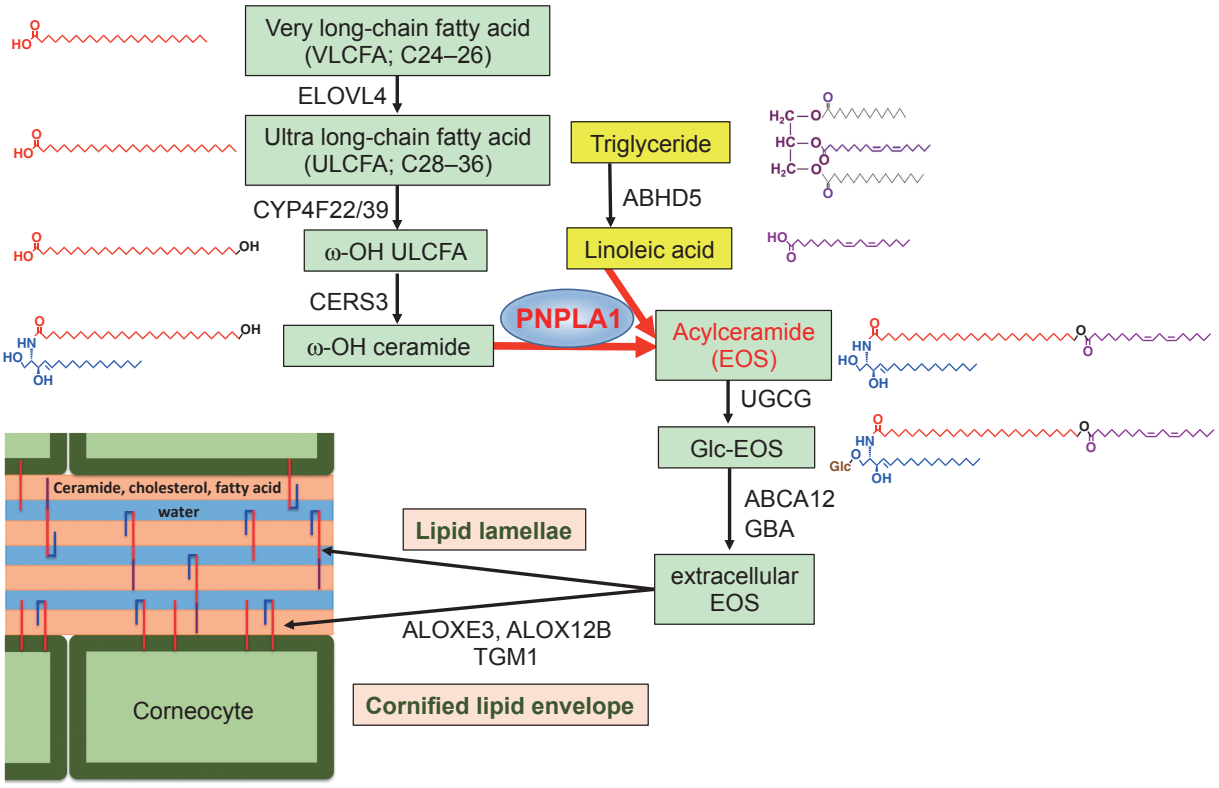

Fig. 5. The role of PNPLA1 in epidermal acylceramide biosynthesis. Structures of the metabolites and enzymes or transporters responsible for individual steps in the acylceramide-biosynthetic pathway are indicated. Mutations or deletions of these enzymes cause ichthyosis in both human and mouse. PNPLA1 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 PLA_2. Lysosomal PLA_2 ($LPLA_2$), also known as group XV PLA_2, is homologous with lecithin cholesterol acyltransferase (LCAT) and catalytically active under mildly acidic conditions.[79] $LPLA_2$ hydrolyzes both *sn*-1 and *sn*-2 fatty acids in phospholipids and contributes to phospholipid degradation in lysosomes. Genetic deletion of $LPLA_2$ 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 PLA_2 (PLA2G16), display PLA_1 and PLA_2 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]

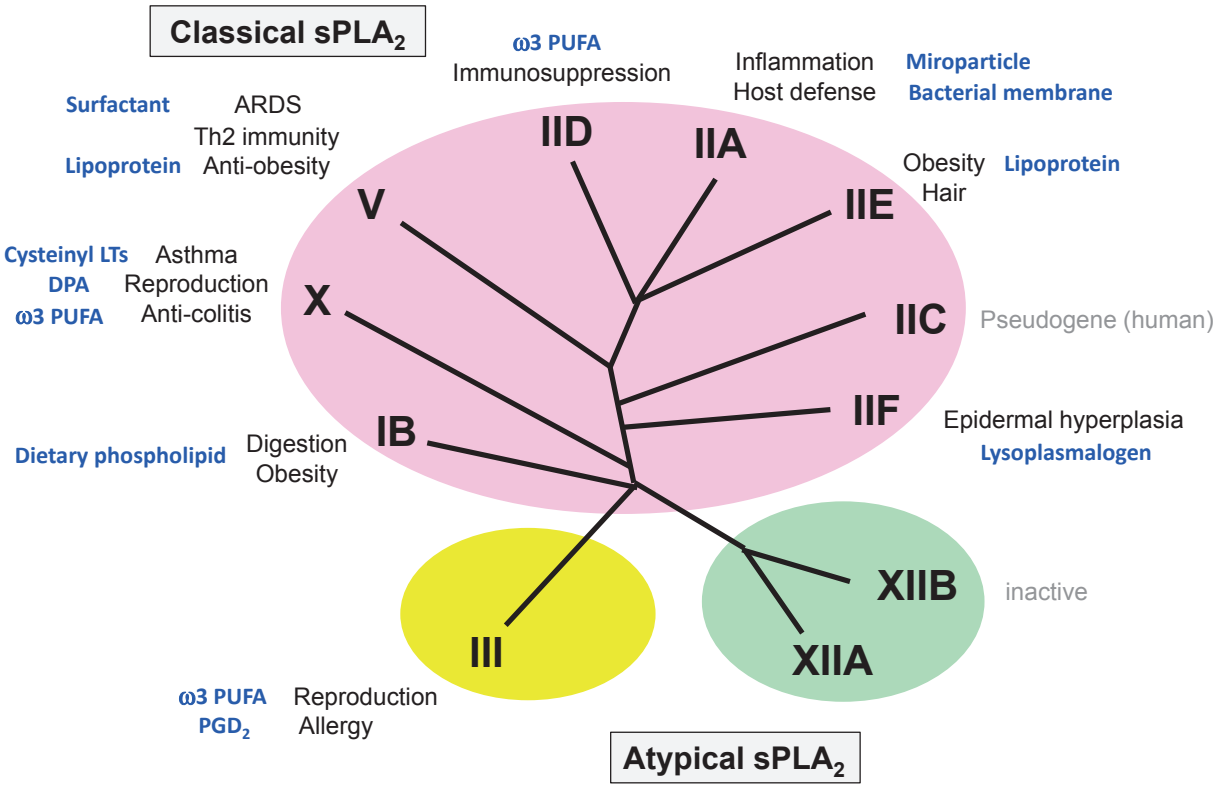

Fig. 6. The $sPLA_2$ family. The phylogenetic tree of $sPLA_2$ isoforms, which are subdivided into classical $sPLA_2$s (I/II/V/X branch) and atypical $sPLA_2$s (III and XII branches), is shown. The pathophysiological roles and related types of lipid metabolism (target substrates or products; shown in 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 $cPLA_2\alpha$ (see above), is linked to the production of a pool of PGE_2 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 PLA_2 (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 PLA_2s

General aspects. The secreted PLA_2 ($sPLA_2$) family contains 10 catalytically active isoforms and one inactive isoform in mammals.[42),99] Based on the structural and evolutional 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 $sPLA_2$ family strictly hydrolyzes the *sn*-2 position of phospholipids, a feature that differs from intracellular PLA_2s that often display PLA_1, lysophospholipase, lipase, or transacylase/acyltransferase activity (see above). Individual $sPLA_2$s exhibit unique tissue and cellular distributions, suggesting their distinct biological roles. As $sPLA_2$s are secreted and require Ca^{2+} 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 sPLA$_2$s have been detailed in several recent reviews.[5),100)] Here, I describe several key features of lipoquality regulation by the sPLA$_2$ family.

In terms of the lipoquality, sPLA$_2$s 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 sPLA$_2$-IB and -IIA, two prototypic sPLA$_2$s 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 PLA$_2$s that belong to group I and II sPLA$_2$s, are capable of releasing fatty acids non-selectively. However, recent lipidomics-based evaluation of the substrate specificity of sPLA$_2$s toward natural membranes (see above) has revealed that several sPLA$_2$s can distinguish *sn*-2 fatty acyl moieties in phospholipids under physiologically relevant conditions. In general terms, sPLA$_2$-IB, -IIA and -IIE do not discriminate fatty acid species, sPLA$_2$-V tends to prefer those with a lower degree of unsaturation such as oleic acid (OA; C18:1), and sPLA$_2$-IID, -IIF, -III and -X tend to prefer PUFAs including AA and DHA. Several sPLA$_2$s can also distinguish differences in the polar head groups of phospholipids. For instance, sPLA$_2$-X is very active on PC, while sPLA$_2$-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 sPLA$_2$s 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 sPLA$_2$s. sPLA$_2$-IB, also known as "pancreatic sPLA$_2$", 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 sPLA$_2$-IB is to digest dietary and biliary phospholipids in the intestinal lumen. Perturbation of this process by gene disruption or pharmacological inhibition of sPLA$_2$-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)]

sPLA$_2$-IIA is often referred to as "inflammatory sPLA$_2$", since its expression is induced by pro-inflammatory cytokines such as TNFα and IL-1β or by bacterial products such as lipopolysaccharide.[110)] In mice, however, sPLA$_2$-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 sPLA$_2$-IIA is the degradation of bacterial membranes, thereby providing the first line of antimicrobial defense in the host.[113),114)] Consistent with this, sPLA$_2$-IIA preferentially hydrolyzes PE and phosphatidylglycerol, which are enriched in bacterial membranes. Under sterile conditions, sPLA$_2$-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 microparticular phospholipids by sPLA$_2$-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, sPLA$_2$-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.

sPLA$_2$-IIA, -IIC, -IID, -IIE and -IIF are often classified into the group II subfamily (sPLA$_2$-IIC is a pseudogene in human), since they share structural characteristics and map to the same chromosome locus. sPLA$_2$-IID is constitutively expressed in dendritic cells (DCs) in lymphoid organs. sPLA$_2$-IID is an "immunosuppressive sPLA$_2$" that attenuates DC-mediated adaptive immunity by hydrolyzing PE probably in microparticles to mobilize anti-inflammatory ω3 PUFAs and their metabolites such as resolvin D1 (RvD1).[7)] As such, sPLA$_2$-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 sPLA$_2$-IIA, which is stimulus-inducible (see above), sPLA$_2$-IID is downregulated by pro-inflammatory stimuli, consistent with its anti-inflammatory role.

In mice, sPLA$_2$-IIE instead of sPLA$_2$-IIA is upregulated in several tissues under inflammatory or other conditions. sPLA$_2$-IIE is expressed in hair follicles in association with the growth phase of the hair cycle[118)] and induced in adipose tissue in

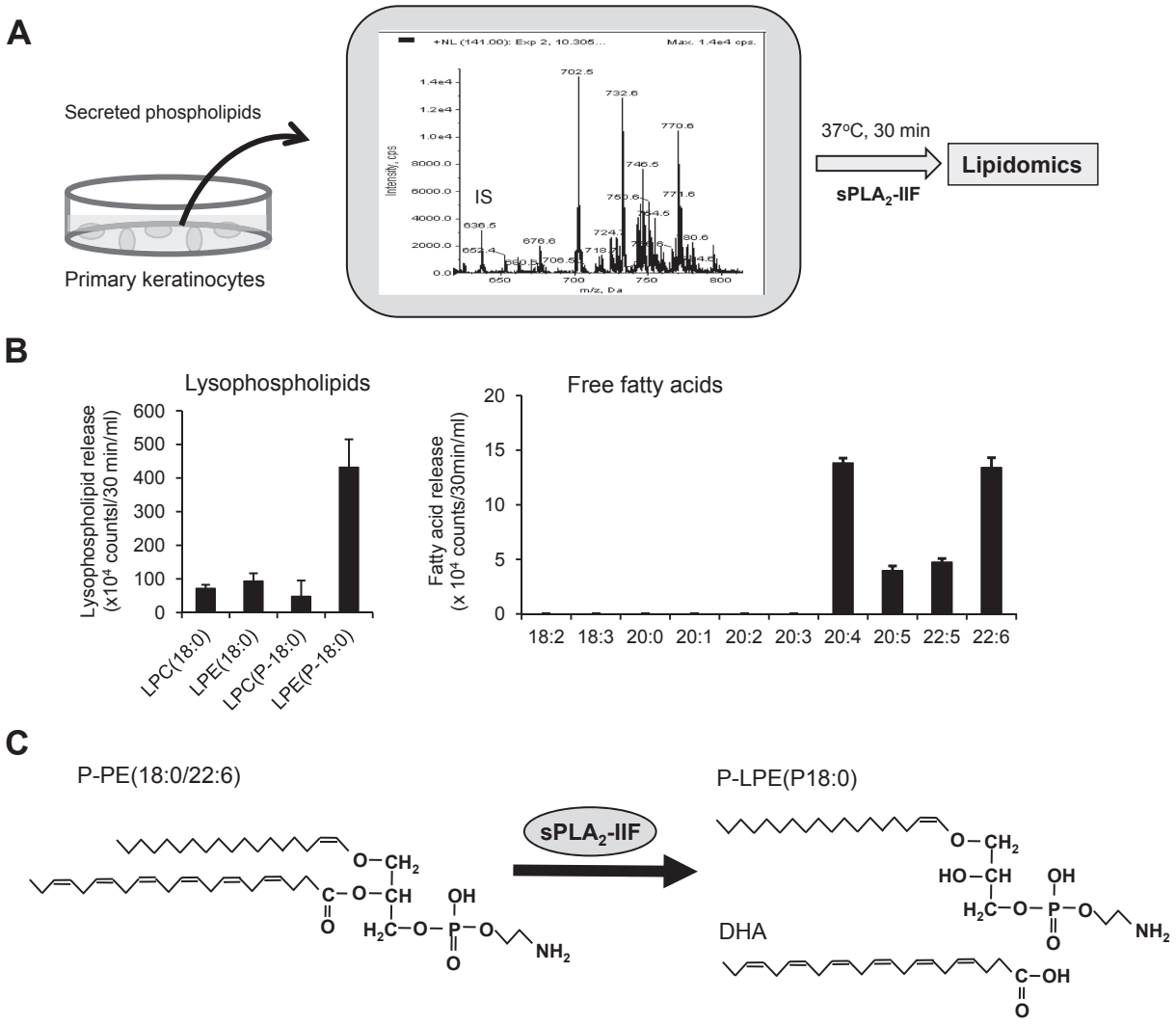

Fig. 7. Properties of $sPLA_2$-IIF. (A) A schematic procedure for identification of the lipid metabolism driven by $sPLA_2$-IIF in differentiating keratinocytes. Phospholipids extracted from the culture supernatants of mouse keratinocytes (a representative mass spectrometric profile of phospholipids is shown; IS, internal standard; cps, count per second) were incubated with a physiologically relevant concentration of recombinant $sPLA_2$-IIF and then taken for the lipidomics analysis. (B) In the assay shown in (A), $sPLA_2$-IIF preferentially increased plasmalogen-type (P-) lysophosphatidylethanolamine (LPE) species as well as PUFAs. Values represent AUC (area under the curve; mean ± SEM, n = 4). (C) The results shown in (B), together with *in vivo* analyses using $sPLA_2$-IIF-transgenic and knockout mice,[6] indicate that $sPLA_2$-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] $sPLA_2$-IIE hydrolyzes PE without apparent fatty acid selectivity in hair follicles and lipoproteins, and accordingly, $sPLA_2$-IIE-deficient mice display subtle abnormalities in hair follicles[118] and are modestly protected from diet-induced obesity and hyperlipidemia.[119]

$sPLA_2$-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 $sPLA_2$s.[120] Physiologically, $sPLA_2$-IIF is an "epidermal $sPLA_2$" that is expressed predominantly in the upper epidermis and induced by IL-22, a Th17 cytokine, in psoriatic skin.[6] $sPLA_2$-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, $sPLA_2$-IIF-null mice are protected against epidermal-hyperplasic diseases such as psor-

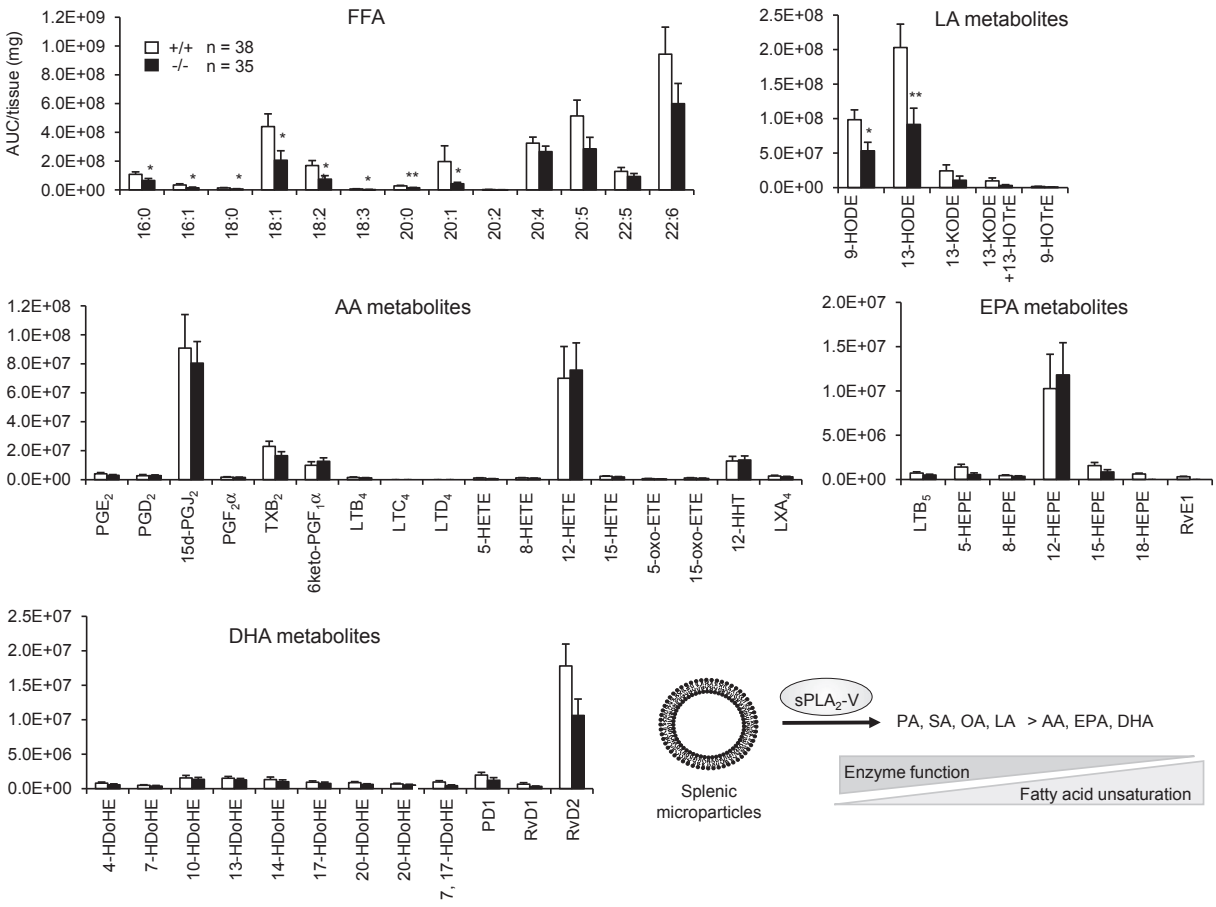

Fig. 8. Fatty acid selectivity of $sPLA_2$-V. Lipids extracted from the spleen of 1-year-old $sPLA_2$-V-deficient (−/−) and littermate control (+/+) mice were subjected to mass spectrometric lipidomics analysis (values are mean ± SEM, $*P < 0.05$ and $**P < 0.01$). Experiments were performed in accordance 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 $sPLA_2$-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 $sPLA_2$-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 $sPLA_2$-IIF-transgenic mice spontaneously develop psoriasis-like skin.[6)]

Although $sPLA_2$-V was previously thought to be a regulator of AA metabolism,[121),122)] it is now becoming obvious that this $sPLA_2$ has a preference for phospholipids having fatty acids with a lower degree of unsaturation. $sPLA_2$-V is markedly induced in adipocytes during obesity as a "metabolic $sPLA_2$" 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 $sPLA_2$-V, but not other $sPLA_2$s, results in neonatal death due to a respiratory defect, which is attributable to the ability of $sPLA_2$-V to potently hydrolyze PC with palmitic acid (PA, C16:0), a major component of lung surfactant.[123)] This unique substrate preference of $sPLA_2$-V has also been supported by a recent lipidomics analysis of the spleen (a tissue where $sPLA_2$-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 $sPLA_2$-V-deficient mice relative to wild-type mice (Fig. 8). This is in contrast to the spleen of $sPLA_2$-IID-deficient mice, in which ω3 PUFAs and their metabolites are selectively diminished,[7)] revealing distinct lipoquality regulation

by different sPLA$_2$s. Another intriguing feature of sPLA$_2$-V is that it is the only "Th2-prone sPLA$_2$" induced in M2 macrophages by the Th2 cytokines IL-4 and IL-13 and promotes Th2-driven pathology such as asthma. Gene ablation of sPLA$_2$-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, sPLA$_2$-V-null macrophages have a reduced ability to phagocytose extracellular materials. Accordingly, sPLA$_2$-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, sPLA$_2$-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 sPLA$_2$s, sPLA$_2$-X has the highest affinity for PC leading to release of fatty acids, with an apparent tendency for PUFA preference. sPLA$_2$-X is activated by cleavage of the *N*-terminal propeptide by furin-type convertases.[128] sPLA$_2$-X is expressed abundantly in colorectal epithelial and goblet cells and has a protective role in colitis by mobilizing anti-inflammatory ω3 PUFAs.[24] Consistently, sPLA$_2$-X-transgenic mice exhibit global anti-inflammatory phenotypes in association with elevation of systemic ω3 PUFA levels.[24] In the process of reproduction, sPLA$_2$-X secreted from the acrosomes of activated spermatozoa hydrolyzes sperm membrane phospholipids to release DHA and docosapentaenioc acid (DPA, C22:5), the latter facilitating fertilization.[24),129] Additionally, sPLA$_2$-X-null mice are protected from asthma, accompanied by decreased levels of pulmonary ω6 AA-derived eicosanoids.[130] Unlike the situation in sPLA$_2$-V-null mice (see above), however, the Th2 response *per se* is not affected in the asthma model[131] and the lung damage is milder following influenza infection[132] in sPLA$_2$-X-null mice, illustrating the distinct actions of different sPLA$_2$s in the same tissue.

Atypical sPLA$_2$s. sPLA$_2$-III is unusual in that it consists of three domains, in which the central sPLA$_2$ domain similar to bee venom group III sPLA$_2$ is flanked by large and unique N- and C-terminal domains.[133] The enzyme is processed to the sPLA$_2$ domain-only form that retains full enzymatic activity.[134] Although sPLA$_2$-III does not discriminate the polar head groups, it tends to prefer *sn*-2 PUFAs in the substrate phospholipids. sPLA$_2$-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] sPLA$_2$-III is also secreted from mast cells and acts on microenvironmental fibroblasts to produce PGD$_2$, which in turn promotes proper maturation of mast cells.[136] Accordingly, mice lacking sPLA$_2$-III exhibit male hypofertility and reduced anaphylactic responses.

sPLA$_2$-XIIA is evolutionally far distant from other sPLA$_2$s.[137] sPLA$_2$-XIIA is expressed in many tissues at relatively high levels, yet its enzymatic activity is weaker than that of other sPLA$_2$s. The properties and physiological roles of sPLA$_2$-XIIA are currently unclear and await future studies using sPLA$_2$-XIIA-deficient mice. Apart from lipoquality regulation, sPLA$_2$-XIIB is a catalytically inactive protein due to substitution of the catalytic center histidine by leucine.[138] sPLA$_2$-XIIB deficiency impairs hepatic lipoprotein secretion,[139] although the mechanism is unclear.

sPLA$_2$ receptor. Beyond the lipoquality control by sPLA$_2$s, several sPLA$_2$s binds to sPLA$_2$ receptor (PLA2R1, also known as the C-type lectin Clec13c) with different affinities.[140] In mice, PLA2R1 binds to sPLA$_2$-IB, -IIA, -IIE, -IIF and -X with high affinity, sPLA$_2$-V with moderate affinity, and sPLA$_2$-IID, -III and -XIIA with low or no affinity.[138] PLA2R1 is homologous to sPLA$_2$-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 sPLA$_2$s, as a signaling receptor that transduces sPLA$_2$-dependent signals in a catalytic activity-independent manner, or as a pleiotropic receptor that binds to non-sPLA$_2$ ligands. In support of its clearance role, *Pla2r1*$^{-/-}$ mice show more severe asthma, likely due to defective clearance of pro-asthmatic sPLA$_2$-X.[141] In support of its signaling role, PLA2R1, probably through binding to myocardial sPLA$_2$s 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 sPLA$_2$-dependent or -independent.

Table 2. Representative PLA_2 mutations in human diseases

Families	PLA_2 genes	Human diseases	References
$cPLA_2$	*PLA2G4A*	Platelet dysfunction, Intestinal ulceration	35
$iPLA_2$	*PNPLA1*	Ichthyosis	177
	PNPLA2	Chanarin-Dorfman syndrome (neutral lipid strage disease with myopathy)	178
	PNPLA3	Non-alchoholic fatty liver disease (NASH, NAFLD)	63
	PNPLA6	Ataxia, Hereditary spastic paraplegia, Boucher-Neuhauser and Gordon Holmes syndromes	179
		Photoreceptor degeneration	53
	PNPLA7	Psychophysiological endophenotype	180
	PNPLA8	Myopathy	51
	PNPLA9/PLA2G6	Parkinson's disease, Infantile neuroaxonal dystrophy (INAD)	49
		Familial melanoma	181
PAFAH	*PAFAH/PLA2G7A*	Cardiovascular disease	182
ABHD	*ABHD5*	Chanarin-Dorfman Syndrome with ichtyosis	98
	ABHD12	PHARC syndrome (polyneuropathy, hearing loss, ataxia, retinitis pigmentosa, and cataract)	97
$sPLA_2$	*PLA2G1B*	Obesity	109
	PLA2G2A	Cardiovascular disease	142, 183
		Gastric cancer	184
	PLA2G2D	Body weight loss in COPD (chronic obstructive pulmonary disease)	185
	PLA2G2E	Ulcerative colitis	186
	PLA2G3	Colorectal cancer	187, 188
		Alzheimer's disease	189
	PLA2G5	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 PLA_2s, 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 PLA_2s acquired from studies using animal models should be translated to humans. Current knowledges on the relationship between PLA_2 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 PLA_2-driven lipid pathways that could be biomarkers or druggable targets for particular diseases.

Acknowledgments

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References

1) Shimizu, T. (2009) Lipid mediators in health and disease: enzymes and receptors as therapeutic targets for the regulation of immunity and inflammation. Annu. Rev. Pharmacol. Toxicol. **49**, 123–150.
2) Narumiya, S. and Furuyashiki, T. (2011) Fever, inflammation, pain and beyond: prostanoid receptor research during these 25 years. FASEB J. **25**, 813–818.
3) Serhan, C.N. (2014) Pro-resolving lipid mediators are leads for resolution physiology. Nature **510**, 92–101.
4) Aikawa, S., Hashimoto, T., Kano, K. and Aoki, J. (2015) Lysophosphatidic acid as a lipid mediator with multiple biological actions. J. Biochem. **157**, 81–89.
5) Yamamoto, K., Miki, Y., Sato, H., Murase, R., Taketomi, Y. and Murakami, M. (2017) Secreted phospholipase A_2 specificity on natural membrane phospholipids. Methods Enzymol. **583**, 101–117.
6) Yamamoto, K., Miki, Y., Sato, M., Taketomi, Y., Nishito, Y., Taya, C., Muramatsu, K., Ikeda, K., Nakanishi, H., Taguchi, R., Kambe, N., Kabashima, K., Lambeau, G., Gelb, M.H. and Murakami, M. (2015) The role of group IIF-secreted phospholipase A_2 in epidermal homeostasis and hyperplasia. J. Exp. Med. **212**, 1901–1919.
7) Miki, Y., Yamamoto, K., Taketomi, Y., Sato, H., Shimo, K., Kobayashi, T., Ishikawa, Y., Ishii, T.,

Nakanishi, H., Ikeda, K., Taguchi, R., Kabashima, K., Arita, M., Arai, H., Lambeau, G., Bollinger, J.M., Hara, S., Gelb, M.H. and Murakami, M. (2013) Lymphoid tissue phospholipase A_2 group IID resolves contact hypersensitivity by driving antiinflammatory lipid mediators. J. Exp. Med. **210**, 1217–1234.

8) Ohto, T., Uozumi, N., Hirabayashi, T. and Shimizu, T. (2005) Identification of novel cytosolic phospholipase A_2s, murine cPLA$_2\delta$, ε, and ζ, which form a gene cluster with cPLA$_2\beta$. J. Biol. Chem. **280**, 24576–24583.

9) Leslie, C.C. (2015) Cytosolic phospholipase A_2: physiological function and role in disease. J. Lipid Res. **56**, 1386–1402.

10) Clark, J.D., Lin, L.L., Kriz, R.W., Ramesha, C.S., Sultzman, L.A., Lin, A.Y., Milona, N. and Knopf, J.L. (1991) A novel arachidonic acid-selective cytosolic PLA_2 contains a Ca^{2+}-dependent translocation domain with homology to PKC and GAP. Cell **65**, 1043–1051.

11) Lin, L.L., Wartmann, M., Lin, A.Y., Knopf, J.L., Seth, A. and Davis, R.J. (1993) cPLA$_2$ is phosphorylated and activated by MAP kinase. Cell **72**, 269–278.

12) Casas, J., Gijon, M.A., Vigo, A.G., Crespo, M.S., Balsinde, J. and Balboa, M.A. (2006) Phosphatidylinositol 4,5-bisphosphate anchors cytosolic group IVA phospholipase A_2 to perinuclear membranes and decreases its calcium requirement for translocation in live cells. Mol. Biol. Cell **17**, 155–162.

13) Stahelin, R.V., Subramanian, P., Vora, M., Cho, W. and Chalfant, C.E. (2007) Ceramide-1-phosphate binds group IVA cytosolic phospholipase A_2 via a novel site in the C2 domain. J. Biol. Chem. **282**, 20467–20474.

14) Bonventre, J.V., Huang, Z., Taheri, M.R., O'Leary, E., Li, E., Moskowitz, M.A. and Sapirstein, A. (1997) Reduced fertility and postischaemic brain injury in mice deficient in cytosolic phospholipase A_2. Nature **390**, 622–625.

15) Uozumi, N., Kume, K., Nagase, T., Nakatani, N., Ishii, S., Tashiro, F., Komagata, Y., Maki, K., Ikuta, K., Ouchi, Y., Miyazaki, J. and Shimizu, T. (1997) Role of cytosolic phospholipase A_2 in allergic response and parturition. Nature **390**, 618–622.

16) Wong, D.A., Kita, Y., Uozumi, N. and Shimizu, T. (2002) Discrete role for cytosolic phospholipase $A_2\alpha$ in platelets: studies using single and double mutant mice of cytosolic and group IIA secretory phospholipase A_2. J. Exp. Med. **196**, 349–357.

17) Haq, S., Kilter, H., Michael, A., Tao, J., O'Leary, E., Sun, X.M., Walters, B., Bhattacharya, K., Chen, X., Cui, L., Andreucci, M., Rosenzweig, A., Guerrero, J.L., Patten, R., Liao, R., Molkentin, J., Picard, M., Bonventre, J.V. and Force, T. (2003) Deletion of cytosolic phospholipase A_2 promotes striated muscle growth. Nat. Med. **9**, 944–951.

18) Le, T.D., Shirai, Y., Okamoto, T., Tatsukawa, T., Nagao, S., Shimizu, T. and Ito, M. (2010) Lipid signaling in cytosolic phospholipase $A_2\alpha$-cyclooxygenase-2 cascade mediates cerebellar long-term depression and motor learning. Proc. Natl. Acad. Sci. U.S.A. **107**, 3198–3203.

19) Nagase, T., Uozumi, N., Ishii, S., Kume, K., Izumi, T., Ouchi, Y. and Shimizu, T. (2000) Acute lung injury by sepsis and acid aspiration: a key role for cytosolic phospholipase A_2. Nat. Immunol. **1**, 42–46.

20) Hegen, M., Sun, L., Uozumi, N., Kume, K., Goad, M.E., Nickerson-Nutter, C.L., Shimizu, T. and Clark, J.D. (2003) Cytosolic phospholipase $A_2\alpha$-deficient mice are resistant to collagen-induced arthritis. J. Exp. Med. **197**, 1297–1302.

21) Miyaura, C., Inada, M., Matsumoto, C., Ohshiba, T., Uozumi, N., Shimizu, T. and Ito, A. (2003) An essential role of cytosolic phospholipase $A_2\alpha$ in prostaglandin E_2-mediated bone resorption associated with inflammation. J. Exp. Med. **197**, 1303–1310.

22) Marusic, S., Leach, M.W., Pelker, J.W., Azoitei, M.L., Uozumi, N., Cui, J., Shen, M.W., DeClercq, C.M., Miyashiro, J.S., Carito, B.A., Thakker, P., Simmons, D.L., Leonard, J.P., Shimizu, T. and Clark, J.D. (2005) Cytosolic phospholipase $A_2\alpha$-deficient mice are resistant to experimental autoimmune encephalomyelitis. J. Exp. Med. **202**, 841–851.

23) Sanchez-Mejia, R.O., Newman, J.W., Toh, S., Yu, G.Q., Zhou, Y., Halabisky, B., Cisse, M., Scearce-Levie, K., Cheng, I.H., Gan, L., Palop, J.J., Bonventre, J.V. and Mucke, L. (2008) Phospholipase A_2 reduction ameliorates cognitive deficits in a mouse model of Alzheimer's disease. Nat. Neurosci. **11**, 1311–1318.

24) Murase, R., Sato, H., Yamamoto, K., Ushida, A., Nishito, Y., Ikeda, K., Kobayashi, T., Yamamoto, T., Taketomi, Y. and Murakami, M. (2016) Group X secreted phospholipase A_2 releases ω3 polyunsaturated fatty acids, suppresses colitis, and promotes sperm fertility. J. Biol. Chem. **291**, 6895–6911.

25) Kim, D.C., Hsu, F.I., Barrett, N.A., Friend, D.S., Grenningloh, R., Ho, I.C., Al-Garawi, A., Lora, J.M., Lam, B.K., Austen, K.F. and Kanaoka, Y. (2006) Cysteinyl leukotrienes regulate Th2 cell-dependent pulmonary inflammation. J. Immunol. **176**, 4440–4448.

26) Tager, A.M., Bromley, S.K., Medoff, B.D., Islam, S.A., Bercury, S.D., Friedrich, E.B., Carafone, A.D., Gerszten, R.E. and Luster, A.D. (2003) Leukotriene B_4 receptor BLT1 mediates early effector T cell recruitment. Nat. Immunol. **4**, 982–990.

27) Matsuoka, T., Hirata, M., Tanaka, H., Takahashi, Y., Murata, T., Kabashima, K., Sugimoto, Y., Kobayashi, T., Ushikubi, F., Aze, Y., Eguchi, N., Urade, Y., Yoshida, N., Kimura, K., Mizoguchi, A., Honda, Y., Nagai, H. and Narumiya, S. (2000) Prostaglandin D_2 as a mediator of allergic asthma. Science **287**, 2013–2017.

28) Esaki, Y., Li, Y., Sakata, D., Yao, C., Segi-Nishida,

E., Matsuoka, T., Fukuda, K. and Narumiya, S. (2010) Dual roles of PGE_2-EP4 signaling in mouse experimental autoimmune encephalomyelitis. Proc. Natl. Acad. Sci. U.S.A. **107**, 12233–12238.
29) Yao, C., Sakata, D., Esaki, Y., Li, Y., Matsuoka, T., Kuroiwa, K., Sugimoto, Y. and Narumiya, S. (2009) Prostaglandin E_2-EP4 signaling promotes immune inflammation through Th1 cell differentiation and Th17 cell expansion. Nat. Med. **15**, 633–640.
30) Sonoshita, M., Takaku, K., Sasaki, N., Sugimoto, Y., Ushikubi, F., Narumiya, S., Oshima, M. and Taketo, M.M. (2001) Acceleration of intestinal polyposis through prostaglandin receptor EP2 in $Apc^{\Delta 716}$ knockout mice. Nat. Med. **7**, 1048–1051.
31) Hoshino, T., Nakaya, T., Homan, T., Tanaka, K., Sugimoto, Y., Araki, W., Narita, M., Narumiya, S., Suzuki, T. and Mizushima, T. (2007) Involvement of prostaglandin E_2 in production of amyloid-β peptides both *in vitro* and *in vivo*. J. Biol. Chem. **282**, 32676–32688.
32) Kabashima, K., Saji, T., Murata, T., Nagamachi, M., Matsuoka, T., Segi, E., Tsuboi, K., Sugimoto, Y., Kobayashi, T., Miyachi, Y., Ichikawa, A. and Narumiya, S. (2002) The prostaglandin receptor EP4 suppresses colitis, mucosal damage and CD4 cell activation in the gut. J. Clin. Invest. **109**, 883–893.
33) Slatter, D.A., Aldrovandi, M., O'Connor, A., Allen, S.M., Brasher, C.J., Murphy, R.C., Mecklemann, S., Ravi, S., Darley-Usmar, V. and O'Donnell, V.B. (2016) Mapping the human platelet lipidome reveals cytosolic phospholipase A_2 as a regulator of mitochondrial bioenergetics during activation. Cell Metab. **23**, 930–944.
34) Adler, D.H., Phillips, J.A. 3rd, Cogan, J.D., Iverson, T.M., Schnetz-Boutaud, N., Stein, J.A., Brenner, D.A., Milne, G.L., Morrow, J.D., Boutaud, O. and Oates, J.A. (2009) The enteropathy of prostaglandin deficiency. J. Gastroenterol. **44** (Suppl 19), 1–7.
35) Adler, D.H., Cogan, J.D., Phillips, J.A. 3rd, Schnetz-Boutaud, N., Milne, G.L., Iverson, T., Stein, J.A., Brenner, D.A., Morrow, J.D., Boutaud, O. and Oates, J.A. (2008) Inherited human $cPLA_2\alpha$ deficiency is associated with impaired eicosanoid biosynthesis, small intestinal ulceration, and platelet dysfunction. J. Clin. Invest. **118**, 2121–2131.
36) Ghomashchi, F., Naika, G.S., Bollinger, J.G., Aloulou, A., Lehr, M., Leslie, C.C. and Gelb, M.H. (2010) Interfacial kinetic and binding properties of mammalian group IVB phospholipase A_2 ($cPLA_2\beta$) and comparison with the other $cPLA_2$ isoforms. J. Biol. Chem. **285**, 36100–36111.
37) Underwood, K.W., Song, C., Kriz, R.W., Chang, X.J., Knopf, J.L. and Lin, L.L. (1998) A novel calcium-independent phospholipase A_2, $cPLA_2\gamma$, that is prenylated and contains homology to $cPLA_2$. J. Biol. Chem. **273**, 21926–21932.
38) Chiba, H., Michibata, H., Wakimoto, K., Seishima, M., Kawasaki, S., Okubo, K., Mitsui, H., Torii, H. and Imai, Y. (2004) Cloning of a gene for a novel epithelium-specific cytosolic phospholipase A_2, $cPLA_2\delta$, induced in psoriatic skin. J. Biol. Chem. **279**, 12890–12897.
39) Ogura, Y., Parsons, W.H., Kamat, S.S. and Cravatt, B.F. (2016) A calcium-dependent acyltransferase that produces *N*-acyl phosphatidylethanolamines. Nat. Chem. Biol. **12**, 669–671.
40) Ghosh, M., Loper, R., Ghomashchi, F., Tucker, D.E., Bonventre, J.V., Gelb, M.H. and Leslie, C.C. (2007) Function, activity, and membrane targeting of cytosolic phospholipase $A_2\zeta$ in mouse lung fibroblasts. J. Biol. Chem. **282**, 11676–11686.
41) Kienesberger, P.C., Oberer, M., Lass, A. and Zechner, R. (2009) Mammalian patatin domain containing proteins: a family with diverse lipolytic activities involved in multiple biological functions. J. Lipid Res. **50** (Suppl), S63–S68.
42) Murakami, M., Taketomi, Y., Miki, Y., Sato, H., Hirabayashi, T. and Yamamoto, K. (2011) Recent progress in phospholipase A_2 research: from cells to animals to humans. Prog. Lipid Res. **50**, 152–192.
43) Tang, J., Kriz, R.W., Wolfman, N., Shaffer, M., Seehra, J. and Jones, S.S. (1997) A novel cytosolic calcium-independent phospholipase A_2 contains eight ankyrin motifs. J. Biol. Chem. **272**, 8567–8575.
44) Larsson, P.K., Claesson, H.E. and Kennedy, B.P. (1998) Multiple splice variants of the human calcium-independent phospholipase A_2 and their effect on enzyme activity. J. Biol. Chem. **273**, 207–214.
45) Liu, X., Moon, S.H., Jenkins, C.M., Sims, H.F. and Gross, R.W. (2016) Cyclooxygenase-2 mediated oxidation of 2-arachidonoyl-lysophospholipids identifies unknown lipid signaling pathways. Cell Chem. Biol. **23**, 1217–1227.
46) Moon, S.H., Jenkins, C.M., Liu, X., Guan, S., Mancuso, D.J. and Gross, R.W. (2012) Activation of mitochondrial calcium-independent phospholipase $A_2\gamma$ ($iPLA_2\gamma$) by divalent cations mediating arachidonate release and production of downstream eicosanoids. J. Biol. Chem. **287**, 14880–14895.
47) Kienesberger, P.C., Lass, A., Preiss-Landl, K., Wolinski, H., Kohlwein, S.D., Zimmermann, R. and Zechner, R. (2008) Identification of an insulin-regulated lysophospholipase with homology to neuropathy target esterase. J. Biol. Chem. **283**, 5908–5917.
48) Quistad, G.B., Barlow, C., Winrow, C.J., Sparks, S.E. and Casida, J.E. (2003) Evidence that mouse brain neuropathy target esterase is a lysophospholipase. Proc. Natl. Acad. Sci. U.S.A. **100**, 7983–7987.
49) Morgan, N.V., Westaway, S.K., Morton, J.E., Gregory, A., Gissen, P., Sonek, S., Cangul, H., Coryell, J., Canham, N., Nardocci, N., Zorzi, G., Pasha, S., Rodriguez, D., Desguerre, I., Mubaidin,

A., Bertini, E., Trembath, R.C., Simonati, A., Schanen, C., Johnson, C.A., Levinson, B., Woods, C.G., Wilmot, B., Kramer, P., Gitschier, J., Maher, E.R. and Hayflick, S.J. (2006) *PLA2G6*, encoding a phospholipase A_2, is mutated in neurodegenerative disorders with high brain iron. Nat. Genet. **38**, 752–754.

50) Mancuso, D.J., Sims, H.F., Yang, K., Kiebish, M.A., Su, X., Jenkins, C.M., Guan, S., Moon, S.H., Pietka, T., Nassir, F., Schappe, T., Moore, K., Han, X., Abumrad, N.A. and Gross, R.W. (2010) Genetic ablation of calcium-independent phospholipase $A_2\gamma$ prevents obesity and insulin resistance during high fat feeding by mitochondrial uncoupling and increased adipocyte fatty acid oxidation. J. Biol. Chem. **285**, 36495–36510.

51) Saunders, C.J., Moon, S.H., Liu, X., Thiffault, I., Coffman, K., LePichon, J.B., Taboada, E., Smith, L.D., Farrow, E.G., Miller, N., Gibson, M., Patterson, M., Kingsmore, S.F. and Gross, R.W. (2015) Loss of function variants in human *PNPLA8* encoding calcium-independent phospholipase $A_2\gamma$ recapitulate the mitochondriopathy of the homologous null mouse. Hum. Mutat. **36**, 301–306.

52) Topaloglu, A.K., Lomniczi, A., Kretzschmar, D., Dissen, G.A., Kotan, L.D., McArdle, C.A., Koc, A.F., Hamel, B.C., Guclu, M., Papatya, E.D., Eren, E., Mengen, E., Gurbuz, F., Cook, M., Castellano, J.M., Kekil, M.B., Mungan, N.O., Yuksel, B. and Ojeda, S.R. (2014) Loss-of-function mutations in *PNPLA6* encoding neuropathy target esterase underlie pubertal failure and neurological deficits in Gordon Holmes syndrome. J. Clin. Endocrinol. Metab. **99**, E2067–E2075.

53) Kmoch, S., Majewski, J., Ramamurthy, V., Cao, S., Fahiminiya, S., Ren, H., MacDonald, I.M., Lopez, I., Sun, V., Keser, V., Khan, A., Stranecky, V., Hartmannova, H., Pristoupilova, A., Hodanova, K., Piherova, L., Kuchar, L., Baxova, A., Chen, R., Barsottini, O.G., Pyle, A., Griffin, H., Splitt, M., Sallum, J., Tolmie, J.L., Sampson, J.R., Chinnery, P., Care4Rare Canada, Banin, E., Sharon, D., Dutta, S., Grebler, R., Helfrich-Foerster, C., Pedroso, J.L., Kretzschmar, D., Cayouette, M. and Koenekoop, R.K. (2015) Mutations in *PNPLA6* are linked to photoreceptor degeneration and various forms of childhood blindness. Nat. Commun. **6**, 5614.

54) Zhou, Q., Yen, A., Rymarczyk, G., Asai, H., Trengrove, C., Aziz, N., Kirber, M.T., Mostoslavsky, G., Ikezu, T., Wolozin, B. and Bolotina, V.M. (2016) Impairment of PARK14-dependent Ca^{2+} signalling is a novel determinant of Parkinson's disease. Nat. Commun. **7**, 10332.

55) Bao, S., Miller, D.J., Ma, Z., Wohltmann, M., Eng, G., Ramanadham, S., Moley, K. and Turk, J. (2004) Male mice that do not express group VIA phospholipase A_2 produce spermatozoa with impaired motility and have greatly reduced fertility. J. Biol. Chem. **279**, 38194–38200.

56) Zimmermann, R., Strauss, J.G., Haemmerle, G., Schoiswohl, G., Birner-Gruenberger, R., Riederer, M., Lass, A., Neuberger, G., Eisenhaber, F., Hermetter, A. and Zechner, R. (2004) Fat mobilization in adipose tissue is promoted by adipose triglyceride lipase. Science **306**, 1383–1386.

57) Haemmerle, G., Lass, A., Zimmermann, R., Gorkiewicz, G., Meyer, C., Rozman, J., Heldmaier, G., Maier, R., Theussl, C., Eder, S., Kratky, D., Wagner, E.F., Klingenspor, M., Hoefler, G. and Zechner, R. (2006) Defective lipolysis and altered energy metabolism in mice lacking adipose triglyceride lipase. Science **312**, 734–737.

58) Das, S.K., Eder, S., Schauer, S., Diwoky, C., Temmel, H., Guertl, B., Gorkiewicz, G., Tamilarasan, K.P., Kumari, P., Trauner, M., Zimmermann, R., Vesely, P., Haemmerle, G., Zechner, R. and Hoefler, G. (2011) Adipose triglyceride lipase contributes to cancer-associated cachexia. Science **333**, 233–238.

59) Yang, X., Lu, X., Lombes, M., Rha, G.B., Chi, Y.I., Guerin, T.M., Smart, E.J. and Liu, J. (2010) The G_0/G_1 switch gene 2 regulates adipose lipolysis through association with adipose triglyceride lipase. Cell Metab. **11**, 194–205.

60) Haemmerle, G., Moustafa, T., Woelkart, G., Buttner, S., Schmidt, A., van de Weijer, T., Hesselink, M., Jaeger, D., Kienesberger, P.C., Zierler, K., Schreiber, R., Eichmann, T., Kolb, D., Kotzbeck, P., Schweiger, M., Kumari, M., Eder, S., Schoiswohl, G., Wongsiriroj, N., Pollak, N.M., Radner, F.P., Preiss-Landl, K., Kolbe, T., Rulicke, T., Pieske, B., Trauner, M., Lass, A., Zimmermann, R., Hoefler, G., Cinti, S., Kershaw, E.E., Schrauwen, P., Madeo, F., Mayer, B. and Zechner, R. (2011) ATGL-mediated fat catabolism regulates cardiac mitochondrial function via PPAR-α and PGC-1. Nat. Med. **17**, 1076–1085.

61) Lass, A., Zimmermann, R., Oberer, M. and Zechner, R. (2011) Lipolysis — a highly regulated multienzyme complex mediates the catabolism of cellular fat stores. Prog. Lipid Res. **50**, 14–27.

62) Young, S.G. and Zechner, R. (2013) Biochemistry and pathophysiology of intravascular and intracellular lipolysis. Genes Dev. **27**, 459–484.

63) Romeo, S., Kozlitina, J., Xing, C., Pertsemlidis, A., Cox, D., Pennacchio, L.A., Boerwinkle, E., Cohen, J.C. and Hobbs, H.H. (2008) Genetic variation in *PNPLA3* confers susceptibility to nonalcoholic fatty liver disease. Nat. Genet. **40**, 1461–1465.

64) Li, J.Z., Huang, Y., Karaman, R., Ivanova, P.T., Brown, H.A., Roddy, T., Castro-Perez, J., Cohen, J.C. and Hobbs, H.H. (2012) Chronic overexpression of $PNPLA3^{I148M}$ in mouse liver causes hepatic steatosis. J. Clin. Invest. **122**, 4130–4144.

65) Huang, Y., He, S., Li, J.Z., Seo, Y.K., Osborne, T.F., Cohen, J.C. and Hobbs, H.H. (2010) A feed-forward loop amplifies nutritional regulation of PNPLA3. Proc. Natl. Acad. Sci. U.S.A. **107**, 7892–7897.

66) Gao, J. and Simon, M. (2005) Identification of a

novel keratinocyte retinyl ester hydrolase as a transacylase and lipase. J. Invest. Dermatol. **124**, 1259–1266.
67) Dupont, N., Chauhan, S., Arko-Mensah, J., Castillo, E.F., Masedunskas, A., Weigert, R., Robenek, H., Proikas-Cezanne, T. and Deretic, V. (2014) Neutral lipid stores and lipase PNPLA5 contribute to autophagosome biogenesis. Curr. Biol. **24**, 609–620.
68) Hirabayashi, T., Anjo, T., Kaneko, A., Senoo, Y., Shibata, A., Takama, H., Yokoyama, K., Nishito, Y., Ono, T., Taya, C., Muramatsu, K., Fukami, K., Munoz-Garcia, A., Brash, A.R., Ikeda, K., Arita, M., Akiyama, M. and Murakami, M. (2017) PNPLA1 has a crucial role in skin barrier function by directing acylceramide biosynthesis. Nat. Commun. **8**, 14609.
69) Ohno, Y., Kamiyama, N., Nakamichi, S. and Kihara, A. (2017) PNPLA1 is a transacylase essential for the generation of the skin barrier lipid ω-O-acylceramide. Nat. Commun. **8**, 14610.
70) Hattori, M. and Arai, H. (2015) Intracellular PAF-acetylhydrolase type I. Enzymes **38**, 23–36.
71) Kono, N. and Arai, H. (2015) Intracellular platelet-activating factor acetylhydrolase, type II: A unique cellular phospholipase A_2 that hydrolyzes oxidatively modified phospholipids. Enzymes **38**, 43–54.
72) Ho, Y.S., Swenson, L., Derewenda, U., Serre, L., Wei, Y., Dauter, Z., Hattori, M., Adachi, T., Aoki, J., Arai, H., Inoue, K. and Derewenda, Z.S. (1997) Brain acetylhydrolase that inactivates platelet-activating factor is a G-protein-like trimer. Nature **385**, 89–93.
73) Koizumi, H., Yamaguchi, N., Hattori, M., Ishikawa, T.O., Aoki, J., Taketo, M.M., Inoue, K. and Arai, H. (2003) Targeted disruption of intracellular type I platelet activating factor-acetylhydrolase catalytic subunits causes severe impairment in spermatogenesis. J. Biol. Chem. **278**, 12489–12494.
74) Kono, N., Inoue, T., Yoshida, Y., Sato, H., Matsusue, T., Itabe, H., Niki, E., Aoki, J. and Arai, H. (2008) Protection against oxidative stress-induced hepatic injury by intracellular type II platelet-activating factor acetylhydrolase by metabolism of oxidized phospholipids *in vivo*. J. Biol. Chem. **283**, 1628–1636.
75) Tjoelker, L.W., Wilder, C., Eberhardt, C., Stafforini, D.M., Dietsch, G., Schimpf, B., Hooper, S., Le Trong, H., Cousens, L.S., Zimmerman, G.A., Yamada, Y., McIntyre, T.M., Prescott, S.M. and Gray, P.W. (1995) Anti-inflammatory properties of a platelet-activating factor acetylhydrolase. Nature **374**, 549–553.
76) Wilensky, R.L., Shi, Y., Mohler, E.R. 3rd, Hamamdzic, D., Burgert, M.E., Li, J., Postle, A., Fenning, R.S., Bollinger, J.G., Hoffman, B.E., Pelchovitz, D.J., Yang, J., Mirabile, R.C., Webb, C.L., Zhang, L., Zhang, P., Gelb, M.H., Walker, M.C., Zalewski, A. and Macphee, C.H. (2008) Inhibition of lipoprotein-associated phospholipase A_2 reduces complex coronary atherosclerotic plaque development. Nat. Med. **14**, 1059–1066.
77) Corson, M.A. (2009) Phospholipase A_2 inhibitors in atherosclerosis: the race is on. Lancet **373**, 608–610.
78) Xu, C., Reichert, E.C., Nakano, T., Lohse, M., Gardner, A.A., Revelo, M.P., Topham, M.K. and Stafforini, D.M. (2013) Deficiency of phospholipase A_2 group 7 decreases intestinal polyposis and colon tumorigenesis in $Apc^{Min/+}$ mice. Cancer Res. **73**, 2806–2816.
79) Abe, A., Hiraoka, M., Wild, S., Wilcoxen, S.E., Paine, R. 3rd and Shayman, J.A. (2004) Lysosomal phospholipase A_2 is selectively expressed in alveolar macrophages. J. Biol. Chem. **279**, 42605–42611.
80) Hiraoka, M., Abe, A., Lu, Y., Yang, K., Han, X., Gross, R.W. and Shayman, J.A. (2006) Lysosomal phospholipase A_2 and phospholipidosis. Mol. Cell. Biol. **26**, 6139–6148.
81) Paduraru, C., Bezbradica, J.S., Kunte, A., Kelly, R., Shayman, J.A., Veerapen, N., Cox, L.R., Besra, G.S. and Cresswell, P. (2013) Role for lysosomal phospholipase A_2 in iNKT cell-mediated CD1d recognition. Proc. Natl. Acad. Sci. U.S.A. **110**, 5097–5102.
82) Schneider, B.E., Behrends, J., Hagens, K., Harmel, N., Shayman, J.A. and Schaible, U.E. (2014) Lysosomal phospholipase A_2: a novel player in host immunity to Mycobacterium tuberculosis. Eur. J. Immunol. **44**, 2394–2404.
83) Uyama, T., Ikematsu, N., Inoue, M., Shinohara, N., Jin, X.H., Tsuboi, K., Tonai, T., Tokumura, A. and Ueda, N. (2012) Generation of *N*-acylphosphatidylethanolamine by members of the phospholipase A/acyltransferase (PLA/AT) family. J. Biol. Chem. **287**, 31905–31919.
84) Jaworski, K., Ahmadian, M., Duncan, R.E., Sarkadi-Nagy, E., Varady, K.A., Hellerstein, M.K., Lee, H.Y., Samuel, V.T., Shulman, G.I., Kim, K.H., de Val, S., Kang, C. and Sul, H.S. (2009) AdPLA ablation increases lipolysis and prevents obesity induced by high-fat feeding or leptin deficiency. Nat. Med. **15**, 159–168.
85) Xiong, S., Tu, H., Kollareddy, M., Pant, V., Li, Q., Zhang, Y., Jackson, J.G., Suh, Y.A., Elizondo-Fraire, A.C., Yang, P., Chau, G., Tashakori, M., Wasylishen, A.R., Ju, Z., Solomon, H., Rotter, V., Liu, B., El-Naggar, A.K., Donehower, L.A., Martinez, L.A. and Lozano, G. (2014) Pla2g16 phospholipase mediates gain-of-function activities of mutant p53. Proc. Natl. Acad. Sci. U.S.A. **111**, 11145–11150.
86) Golczak, M., Sears, A.E., Kiser, P.D. and Palczewski, K. (2015) LRAT-specific domain facilitates vitamin A metabolism by domain swapping in HRASLS3. Nat. Chem. Biol. **11**, 26–32.
87) Uyama, T., Kawai, K., Kono, N., Watanabe, M., Tsuboi, K., Inoue, T., Araki, N., Arai, H. and Ueda, N. (2015) Interaction of phospholipase A/acyltransferase-3 with Pex19p: a possible involve-

ment in the down-regulation of peroxisomes. J. Biol. Chem. **290**, 17520–17534.
88) Staring, J., von Castelmur, E., Blomen, V.A., van den Hengel, L.G., Brockmann, M., Baggen, J., Thibaut, H.J., Nieuwenhuis, J., Janssen, H., van Kuppeveld, F.J., Perrakis, A., Carette, J.E. and Brummelkamp, T.R. (2017) PLA2G16 represents a switch between entry and clearance of Picornaviridae. Nature **541**, 412–416.
89) Thomas, G., Brown, A.L. and Brown, J.M. (2014) *In vivo* metabolite profiling as a means to identify uncharacterized lipase function: recent success stories within the alpha beta hydrolase domain (ABHD) enzyme family. Biochim. Biophys. Acta **1841**, 1097–1101.
90) Long, J.Z., Cisar, J.S., Milliken, D., Niessen, S., Wang, C., Trauger, S.A., Siuzdak, G. and Cravatt, B.F. (2011) Metabolomics annotates ABHD3 as a physiologic regulator of medium-chain phospholipids. Nat. Chem. Biol. **7**, 763–765.
91) Lee, H.C., Simon, G.M. and Cravatt, B.F. (2015) ABHD4 regulates multiple classes of *N*-acyl phospholipids in the mammalian central nervous system. Biochemistry **54**, 2539–2549.
92) Marrs, W.R., Blankman, J.L., Horne, E.A., Thomazeau, A., Lin, Y.H., Coy, J., Bodor, A.L., Muccioli, G.G., Hu, S.S., Woodruff, G., Fung, S., Lafourcade, M., Alexander, J.P., Long, J.Z., Li, W., Xu, C., Moller, T., Mackie, K., Manzoni, O.J., Cravatt, B.F. and Stella, N. (2010) The serine hydrolase ABHD6 controls the accumulation and efficacy of 2-AG at cannabinoid receptors. Nat. Neurosci. **13**, 951–957.
93) Thomas, G., Betters, J.L., Lord, C.C., Brown, A.L., Marshall, S., Ferguson, D., Sawyer, J., Davis, M.A., Melchior, J.T., Blume, L.C., Howlett, A.C., Ivanova, P.T., Milne, S.B., Myers, D.S., Mrak, I., Leber, V., Heier, C., Taschler, U., Blankman, J.L., Cravatt, B.F., Lee, R.G., Crooke, R.M., Graham, M.J., Zimmermann, R., Brown, H.A. and Brown, J.M. (2013) The serine hydrolase ABHD6 Is a critical regulator of the metabolic syndrome. Cell Rep. **5**, 508–520.
94) Tanimura, A., Yamazaki, M., Hashimotodani, Y., Uchigashima, M., Kawata, S., Abe, M., Kita, Y., Hashimoto, K., Shimizu, T., Watanabe, M., Sakimura, K. and Kano, M. (2010) The endocannabinoid 2-arachidonoylglycerol produced by diacylglycerol lipase α mediates retrograde suppression of synaptic transmission. Neuron **65**, 320–327.
95) Kita, Y., Yoshida, K., Tokuoka, S.M., Hamano, F., Yamazaki, M., Sakimura, K., Kano, M. and Shimizu, T. (2015) Fever is mediated by conversion of endocannabinoid 2-arachidonoylglycerol to prostaglandin E_2. PLoS One **10**, e0133663.
96) Kamat, S.S., Camara, K., Parsons, W.H., Chen, D.H., Dix, M.M., Bird, T.D., Howell, A.R. and Cravatt, B.F. (2015) Immunomodulatory lysophosphatidylserines are regulated by ABHD16A and ABHD12 interplay. Nat. Chem. Biol. **11**, 164–171.
97) Blankman, J.L., Long, J.Z., Trauger, S.A., Siuzdak, G. and Cravatt, B.F. (2013) ABHD12 controls brain lysophosphatidylserine pathways that are deregulated in a murine model of the neurodegenerative disease PHARC. Proc. Natl. Acad. Sci. U.S.A. **110**, 1500–1505.
98) Lass, A., Zimmermann, R., Haemmerle, G., Riederer, M., Schoiswohl, G., Schweiger, M., Kienesberger, P., Strauss, J.G., Gorkiewicz, G. and Zechner, R. (2006) Adipose triglyceride lipase-mediated lipolysis of cellular fat stores is activated by CGI-58 and defective in Chanarin-Dorfman Syndrome. Cell Metab. **3**, 309–319.
99) Murakami, M., Sato, H., Miki, Y., Yamamoto, K. and Taketomi, Y. (2015) A new era of secreted phospholipase A_2. J. Lipid Res. **56**, 1248–1261.
100) Murakami, M., Yamamoto, K., Miki, Y., Murase, R., Sato, H. and Taketomi, Y. (2016) The roles of the secreted phospholipase A_2 gene family in immunology. Adv. Immunol. **132**, 91–134.
101) Seilhamer, J.J., Randall, T.L., Yamanaka, M. and Johnson, L.K. (1986) Pancreatic phospholipase A_2: isolation of the human gene and cDNAs from porcine pancreas and human lung. DNA **5**, 519–527.
102) Seilhamer, J.J., Pruzanski, W., Vadas, P., Plant, S., Miller, J.A., Kloss, J. and Johnson, L.K. (1989) Cloning and recombinant expression of phospholipase A_2 present in rheumatoid arthritic synovial fluid. J. Biol. Chem. **264**, 5335–5338.
103) Pan, Y.H., Yu, B.Z., Singer, A.G., Ghomashchi, F., Lambeau, G., Gelb, M.H., Jain, M.K. and Bahnson, B.J. (2002) Crystal structure of human group X secreted phospholipase A_2. Electrostatically neutral interfacial surface targets zwitterionic membranes. J. Biol. Chem. **277**, 29086–29093.
104) Scott, D.L., White, S.P., Browning, J.L., Rosa, J.J., Gelb, M.H. and Sigler, P.B. (1991) Structures of free and inhibited human secretory phospholipase A_2 from inflammatory exudate. Science **254**, 1007–1010.
105) Huggins, K.W., Boileau, A.C. and Hui, D.Y. (2002) Protection against diet-induced obesity and obesity-related insulin resistance in Group 1B PLA_2-deficient mice. Am. J. Physiol. Endocrinol. Metab. **283**, E994–E1001.
106) Labonte, E.D., Kirby, R.J., Schildmeyer, N.M., Cannon, A.M., Huggins, K.W. and Hui, D.Y. (2006) Group 1B phospholipase A_2-mediated lysophospholipid absorption directly contributes to postprandial hyperglycemia. Diabetes **55**, 935–941.
107) Hui, D.Y., Cope, M.J., Labonte, E.D., Chang, H.T., Shao, J., Goka, E., Abousalham, A., Charmot, D. and Buysse, J. (2009) The phospholipase A_2 inhibitor methyl indoxam suppresses diet-induced obesity and glucose intolerance in mice. Br. J. Pharmacol. **157**, 1263–1269.
108) Hollie, N.I., Konaniah, E.S., Goodin, C. and Hui, D.Y. (2014) Group 1B phospholipase A_2 inactivation suppresses atherosclerosis and metabolic

diseases in LDL receptor-deficient mice. Atherosclerosis **234**, 377–380.
109) Wilson, S.G., Adam, G., Langdown, M., Reneland, R., Braun, A., Andrew, T., Surdulescu, G.L., Norberg, M., Dudbridge, F., Reed, P.W., Sambrook, P.N., Kleyn, P.W. and Spector, T.D. (2006) Linkage and potential association of obesity-related phenotypes with two genes on chromosome 12q24 in a female dizygous twin cohort. Eur. J. Hum. Genet. **14**, 340–348.
110) Pruzanski, W. and Vadas, P. (1991) Phospholipase A_2 — a mediator between proximal and distal effectors of inflammation. Immunol. Today **12**, 143–146.
111) Kennedy, B.P., Payette, P., Mudgett, J., Vadas, P., Pruzanski, W., Kwan, M., Tang, C., Rancourt, D.E. and Cromlish, W.A. (1995) A natural disruption of the secretory group II phospholipase A_2 gene in inbred mouse strains. J. Biol. Chem. **270**, 22378–22385.
112) MacPhee, M., Chepenik, K.P., Liddell, R.A., Nelson, K.K., Siracusa, L.D. and Buchberg, A.M. (1995) The secretory phospholipase A_2 gene is a candidate for the *Mom1* locus, a major modifier of Apc^{Min}-induced intestinal neoplasia. Cell **81**, 957–966.
113) Weinrauch, Y., Abad, C., Liang, N.S., Lowry, S.F. and Weiss, J. (1998) Mobilization of potent plasma bactericidal activity during systemic bacterial challenge. Role of group IIA phospholipase A_2. J. Clin. Invest. **102**, 633–638.
114) Pernet, E., Brunet, J., Guillemot, L., Chignard, M., Touqui, L. and Wu, Y. (2015) *Staphylococcus aureus* adenosine inhibits $sPLA_2$-IIA-mediated host killing in the airways. J. Immunol. **194**, 5312–5319.
115) Boudreau, L.H., Duchez, A.C., Cloutier, N., Soulet, D., Martin, N., Bollinger, J., Pare, A., Rousseau, M., Naika, G.S., Levesque, T., Laflamme, C., Marcoux, G., Lambeau, G., Farndale, R.W., Pouliot, M., Hamzeh-Cognasse, H., Cognasse, F., Garraud, O., Nigrovic, P.A., Guderley, H., Lacroix, S., Thibault, L., Semple, J.W., Gelb, M.H. and Boilard, E. (2014) Platelets release mitochondria serving as substrate for bactericidal group IIA-secreted phospholipase A_2 to promote inflammation. Blood **124**, 2173–2183.
116) Miki, Y., Kidoguchi, Y., Sato, M., Taketomi, Y., Taya, C., Muramatsu, K., Gelb, M.H., Yamamoto, K. and Murakami, M. (2016) Dual roles of group IID phospholipase A_2 in inflammation and cancer. J. Biol. Chem. **291**, 15588–15601.
117) Vijay, R., Hua, X., Meyerholz, D.K., Miki, Y., Yamamoto, K., Gelb, M., Murakami, M. and Perlman, S. (2015) Critical role of phospholipase A_2 group IID in age-related susceptibility to severe acute respiratory syndrome-CoV infection. J. Exp. Med. **212**, 1851–1868.
118) Yamamoto, K., Miki, Y., Sato, H., Nishito, Y., Gelb, M.H., Taketomi, Y. and Murakami, M. (2016) Expression and function of group IIE phospholipase A_2 in mouse skin. J. Biol. Chem. **291**, 15602–15613.
119) Sato, H., Taketomi, Y., Ushida, A., Isogai, Y., Kojima, T., Hirabayashi, T., Miki, Y., Yamamoto, K., Nishito, Y., Kobayashi, T., Ikeda, K., Taguchi, R., Hara, S., Ida, S., Miyamoto, Y., Watanabe, M., Baba, H., Miyata, K., Oike, Y., Gelb, M.H. and Murakami, M. (2014) The adipocyte-inducible secreted phospholipases PLA2G5 and PLA2G2E play distinct roles in obesity. Cell Metab. **20**, 119–132.
120) Valentin, E., Ghomashchi, F., Gelb, M.H., Lazdunski, M. and Lambeau, G. (1999) On the diversity of secreted phospholipases A_2. Cloning, tissue distribution, and functional expression of two novel mouse group II enzymes. J. Biol. Chem. **274**, 31195–31202.
121) Murakami, M., Shimbara, S., Kambe, T., Kuwata, H., Winstead, M.V., Tischfield, J.A. and Kudo, I. (1998) The functions of five distinct mammalian phospholipase A_2s in regulating arachidonic acid release. Type IIa and type V secretory phospholipase A_2s are functionally redundant and act in concert with cytosolic phospholipase A_2. J. Biol. Chem. **273**, 14411–14423.
122) Shinohara, H., Balboa, M.A., Johnson, C.A., Balsinde, J. and Dennis, E.A. (1999) Regulation of delayed prostaglandin production in activated P388D1 macrophages by group IV cytosolic and group V secretory phospholipase A_2s. J. Biol. Chem. **274**, 12263–12268.
123) Ohtsuki, M., Taketomi, Y., Arata, S., Masuda, S., Ishikawa, Y., Ishii, T., Takanezawa, Y., Aoki, J., Arai, H., Yamamoto, K., Kudo, I. and Murakami, M. (2006) Transgenic expression of group V, but not group X, secreted phospholipase A_2 in mice leads to neonatal lethality because of lung dysfunction. J. Biol. Chem. **281**, 36420–36433.
124) Ohta, S., Imamura, M., Xing, W., Boyce, J.A. and Balestrieri, B. (2013) Group V secretory phospholipase A_2 is involved in macrophage activation and is sufficient for macrophage effector functions in allergic pulmonary inflammation. J. Immunol. **190**, 5927–5938.
125) Balestrieri, B., Maekawa, A., Xing, W., Gelb, M.H., Katz, H.R. and Arm, J.P. (2009) Group V secretory phospholipase A_2 modulates phagosome maturation and regulates the innate immune response against *Candida albicans*. J. Immunol. **182**, 4891–4898.
126) Boilard, E., Lai, Y., Larabee, K., Balestrieri, B., Ghomashchi, F., Fujioka, D., Gobezie, R., Coblyn, J.S., Weinblatt, M.E., Massarotti, E.M., Thornhill, T.S., Divangahi, M., Remold, H., Lambeau, G., Gelb, M.H., Arm, J.P. and Lee, D.M. (2010) A novel anti-inflammatory role for secretory phospholipase A_2 in immune complex-mediated arthritis. EMBO Mol. Med. **2**, 172–187.
127) Degousee, N., Kelvin, D.J., Geisslinger, G., Hwang, D.M., Stefanski, E., Wang, X.H., Danesh, A., Angioni, C., Schmidt, H., Lindsay, T.F., Gelb, M.H., Bollinger, J., Payre, C., Lambeau, G., Arm, J.P., Keating, A. and Rubin, B.B. (2011)

Group V phospholipase A_2 in bone marrow-derived myeloid cells and bronchial epithelial cells promotes bacterial clearance after *Escherichia coli* pneumonia. J. Biol. Chem. **286**, 35650–35662.

128) Jemel, I., Ii, H., Oslund, R.C., Payre, C., Dabert-Gay, A.S., Douguet, D., Chargui, K., Scarzello, S., Gelb, M.H. and Lambeau, G. (2011) Group X secreted phospholipase A_2 proenzyme is matured by a furin-like proprotein convertase and releases arachidonic acid inside of human HEK293 cells. J. Biol. Chem. **286**, 36509–36521.

129) Escoffier, J., Jemel, I., Tanemoto, A., Taketomi, Y., Payre, C., Coatrieux, C., Sato, H., Yamamoto, K., Masuda, S., Pernet-Gallay, K., Pierre, V., Hara, S., Murakami, M., De Waard, M., Lambeau, G. and Arnoult, C. (2010) Group X phospholipase A_2 is released during sperm acrosome reaction and controls fertility outcome in mice. J. Clin. Invest. **120**, 1415–1428.

130) Henderson, W.R. Jr., Chi, E.Y., Bollinger, J.G., Tien, Y.T., Ye, X., Castelli, L., Rubtsov, Y.P., Singer, A.G., Chiang, G.K., Nevalainen, T., Rudensky, A.Y. and Gelb, M.H. (2007) Importance of group X-secreted phospholipase A_2 in allergen-induced airway inflammation and remodeling in a mouse asthma model. J. Exp. Med. **204**, 865–877.

131) Henderson, W.R. Jr., Ye, X., Lai, Y., Ni, Z., Bollinger, J.G., Tien, Y.T., Chi, E.Y. and Gelb, M.H. (2013) Key role of group v secreted phospholipase A_2 in Th2 cytokine and dendritic cell-driven airway hyperresponsiveness and remodeling. PLoS One **8**, e56172.

132) Kelvin, A.A., Degousee, N., Banner, D., Stefanski, E., Leomicronn, A.J., Angoulvant, D., Paquette, S.G., Huang, S.S., Danesh, A., Robbins, C.S., Noyan, H., Husain, M., Lambeau, G., Gelb, M., Kelvin, D.J. and Rubin, B.B. (2014) Lack of group X secreted phospholipase A_2 increases survival following pandemic H1N1 influenza infection. Virology **454–455**, 78–92.

133) Valentin, E., Ghomashchi, F., Gelb, M.H., Lazdunski, M. and Lambeau, G. (2000) Novel human secreted phospholipase A_2 with homology to the group III bee venom enzyme. J. Biol. Chem. **275**, 7492–7496.

134) Murakami, M., Masuda, S., Shimbara, S., Bezzine, S., Lazdunski, M., Lambeau, G., Gelb, M.H., Matsukura, S., Kokubu, F., Adachi, M. and Kudo, I. (2003) Cellular arachidonate-releasing function of novel classes of secretory phospholipase A_2s (groups III and XII). J. Biol. Chem. **278**, 10657–10667.

135) Sato, H., Taketomi, Y., Isogai, Y., Miki, Y., Yamamoto, K., Masuda, S., Hosono, T., Arata, S., Ishikawa, Y., Ishii, T., Kobayashi, T., Nakanishi, H., Ikeda, K., Taguchi, R., Hara, S., Kudo, I. and Murakami, M. (2010) Group III secreted phospholipase A_2 regulates epididymal sperm maturation and fertility in mice. J. Clin. Invest. **120**, 1400–1414.

136) Taketomi, Y., Ueno, N., Kojima, T., Sato, H., Murase, R., Yamamoto, K., Tanaka, S., Sakanaka, M., Nakamura, M., Nishito, Y., Kawana, M., Kambe, N., Ikeda, K., Taguchi, R., Nakamizo, S., Kabashima, K., Gelb, M.H., Arita, M., Yokomizo, T., Nakamura, M., Watanabe, K., Hirai, H., Nakamura, M., Okayama, Y., Ra, C., Aritake, K., Urade, Y., Morimoto, K., Sugimoto, Y., Shimizu, T., Narumiya, S., Hara, S. and Murakami, M. (2013) Mast cell maturation is driven via a group III phospholipase A_2-prostaglandin D_2-DP1 receptor paracrine axis. Nat. Immunol. **14**, 554–563.

137) Gelb, M.H., Valentin, E., Ghomashchi, F., Lazdunski, M. and Lambeau, G. (2000) Cloning and recombinant expression of a structurally novel human secreted phospholipase A_2. J. Biol. Chem. **275**, 39823–39826.

138) Rouault, M., Bollinger, J.G., Lazdunski, M., Gelb, M.H. and Lambeau, G. (2003) Novel mammalian group XII secreted phospholipase A_2 lacking enzymatic activity. Biochemistry **42**, 11494–11503.

139) Guan, M., Qu, L., Tan, W., Chen, L. and Wong, C.W. (2011) Hepatocyte nuclear factor-4α regulates liver triglyceride metabolism in part through secreted phospholipase A_2 GXIIB. Hepatology **53**, 458–466.

140) Lambeau, G. and Gelb, M.H. (2008) Biochemistry and physiology of mammalian secreted phospholipases A_2. Annu. Rev. Biochem. **77**, 495–520.

141) Tamaru, S., Mishina, H., Watanabe, Y., Watanabe, K., Fujioka, D., Takahashi, S., Suzuki, K., Nakamura, T., Obata, J.E., Kawabata, K., Yokota, Y., Murakami, M., Hanasaki, K. and Kugiyama, K. (2013) Deficiency of phospholipase A_2 receptor exacerbates ovalbumin-induced lung inflammation. J. Immunol. **191**, 1021–1028.

142) Kugiyama, K., Ota, Y., Takazoe, K., Moriyama, Y., Kawano, H., Miyao, Y., Sakamoto, T., Soejima, H., Ogawa, H., Doi, H., Sugiyama, S. and Yasue, H. (1999) Circulating levels of secretory type II phospholipase A_2 predict coronary events in patients with coronary artery disease. Circulation **100**, 1280–1284.

143) Tomas, N.M., Beck, L.H. Jr., Meyer-Schwesinger, C., Seitz-Polski, B., Ma, H., Zahner, G., Dolla, G., Hoxha, E., Helmchen, U., Dabert-Gay, A.S., Debayle, D., Merchant, M., Klein, J., Salant, D.J., Stahl, R.A. and Lambeau, G. (2014) Thrombospondin type-1 domain-containing 7A in idiopathic membranous nephropathy. N. Engl. J. Med. **371**, 2277–2287.

144) Chandak, P.G., Radovic, B., Aflaki, E., Kolb, D., Buchebner, M., Frohlich, E., Magnes, C., Sinner, F., Haemmerle, G., Zechner, R., Tabas, I., Levak-Frank, S. and Kratky, D. (2010) Efficient phagocytosis requires triacylglycerol hydrolysis by adipose triglyceride lipase. J. Biol. Chem. **285**, 20192–20201.

145) Tang, T., Abbott, M.J., Ahmadian, M., Lopes, A.B., Wang, Y. and Sul, H.S. (2013) Desnutrin/ATGL activates PPARδ to promote mitochon-

drial function for insulin secretion in islet β cells. Cell Metab. **18**, 883–895.
146) Ochi, T., Munekage, K., Ono, M., Higuchi, T., Tsuda, M., Hayashi, Y., Okamoto, N., Toda, K., Sakamoto, S., Oben, J.A. and Saibara, T. (2016) Patatin-like phospholipase domain-containing protein 3 is involved in hepatic fatty acid and triglyceride metabolism through X-box binding protein 1 and modulation of endoplasmic reticulum stress in mice. Hepatol. Res. **46**, 584–592.
147) Chen, W., Chang, B., Li, L. and Chan, L. (2010) Patatin-like phospholipase domain-containing 3/adiponutrin deficiency in mice is not associated with fatty liver disease. Hepatology **52**, 1134–1142.
148) Akassoglou, K., Malester, B., Xu, J., Tessarollo, L., Rosenbluth, J. and Chao, M.V. (2004) Brain-specific deletion of neuropathy target esterase/*swisscheese* results in neurodegeneration. Proc. Natl. Acad. Sci. U.S.A. **101**, 5075–5080.
149) Yoda, E., Rai, K., Ogawa, M., Takakura, Y., Kuwata, H., Suzuki, H., Nakatani, Y., Murakami, M. and Hara, S. (2014) Group VIB calcium-independent phospholipase A_2 (iPLA$_2\gamma$) regulates platelet activation, hemostasis and thrombosis in mice. PLoS One **9**, e109409.
150) Yoda, E., Hachisu, K., Taketomi, Y., Yoshida, K., Nakamura, M., Ikeda, K., Taguchi, R., Nakatani, Y., Kuwata, H., Murakami, M., Kudo, I. and Hara, S. (2010) Mitochondrial dysfunction and reduced prostaglandin synthesis in skeletal muscle of Group VIB Ca^{2+}-independent phospholipase $A_2\gamma$-deficient mice. J. Lipid Res. **51**, 3003–3015.
151) Song, H., Wohltmann, M., Bao, S., Ladenson, J.H., Semenkovich, C.F. and Turk, J. (2010) Mice deficient in group VIB phospholipase A_2 (iPLA$_2\gamma$) exhibit relative resistance to obesity and metabolic abnormalities induced by a Western diet. Am. J. Physiol. Endocrinol. Metab. **298**, E1097–E1114.
152) Mancuso, D.J., Kotzbauer, P., Wozniak, D.F., Sims, H.F., Jenkins, C.M., Guan, S., Han, X., Yang, K., Sun, G., Malik, I., Conyers, S., Green, K.G., Schmidt, R.E. and Gross, R.W. (2009) Genetic ablation of calcium-independent phospholipase $A_2\gamma$ leads to alterations in hippocampal cardiolipin content and molecular species distribution, mitochondrial degeneration, autophagy, and cognitive dysfunction. J. Biol. Chem. **284**, 35632–35644.
153) Mancuso, D.J., Sims, H.F., Han, X., Jenkins, C.M., Guan, S.P., Yang, K., Moon, S.H., Pietka, T., Abumrad, N.A., Schlesinger, P.H. and Gross, R.W. (2007) Genetic ablation of calcium-independent phospholipase $A_2\gamma$ leads to alterations in mitochondrial lipid metabolism and function resulting in a deficient mitochondrial bioenergetic phenotype. J. Biol. Chem. **282**, 34611–34622.
154) Moon, S.H., Jenkins, C.M., Mancuso, D.J., Turk, J. and Gross, R.W. (2008) Smooth muscle cell arachidonic acid release, migration, and proliferation are markedly attenuated in mice null for calcium-independent phospholipase $A_2\beta$. J. Biol. Chem. **283**, 33975–33987.
155) Ramanadham, S., Yarasheski, K.E., Silva, M.J., Wohltmann, M., Novack, D.V., Christiansen, B., Tu, X., Zhang, S., Lei, X. and Turk, J. (2008) Age-related changes in bone morphology are accelerated in group VIA phospholipase A_2 (iPLA$_2\beta$)-null mice. Am. J. Pathol. **172**, 868–881.
156) Shinzawa, K., Sumi, H., Ikawa, M., Matsuoka, Y., Okabe, M., Sakoda, S. and Tsujimoto, Y. (2008) Neuroaxonal dystrophy caused by group VIA phospholipase A_2 deficiency in mice: a model of human neurodegenerative disease. J. Neurosci. **28**, 2212–2220.
157) Li, H., Zhao, Z., Wei, G., Yan, L., Wang, D., Zhang, H., Sandusky, G.E., Turk, J. and Xu, Y. (2010) Group VIA phospholipase A_2 in both host and tumor cells is involved in ovarian cancer development. FASEB J. **24**, 4103–4116.
158) McHowat, J., Gullickson, G., Hoover, R.G., Sharma, J., Turk, J. and Kornbluth, J. (2011) Platelet-activating factor and metastasis: calcium-independent phospholipase $A_2\beta$ deficiency protects against breast cancer metastasis to the lung. Am. J. Physiol. Cell Physiol. **300**, C825–C832.
159) Page, R.M., Munch, A., Horn, T., Kuhn, P.H., Colombo, A., Reiner, O., Boutros, M., Steiner, H., Lichtenthaler, S.F. and Haass, C. (2012) Loss of PAFAH1B2 reduces amyloid-β generation by promoting the degradation of amyloid precursor protein C-terminal fragments. J. Neurosci. **32**, 18204–18214.
160) Livnat, I., Finkelshtein, D., Ghosh, I., Arai, H. and Reiner, O. (2010) PAF-AH catalytic subunits modulate the Wnt pathway in developing GABAergic neurons. Front. Cell. Neurosci. **4**, 19.
161) Miyata, K., Oike, Y., Hoshii, T., Maekawa, H., Ogawa, H., Suda, T., Araki, K. and Yamamura, K. (2005) Increase of smooth muscle cell migration and of intimal hyperplasia in mice lacking the α/β hydrolase domain containing 2 gene. Biochem. Biophys. Res. Commun. **329**, 296–304.
162) Jin, S., Zhao, G., Li, Z., Nishimoto, Y., Isohama, Y., Shen, J., Ito, T., Takeya, M., Araki, K., He, P. and Yamamura, K. (2009) Age-related pulmonary emphysema in mice lacking α/β hydrolase domain containing 2 gene. Biochem. Biophys. Res. Commun. **380**, 419–424.
163) Grond, S., Radner, F.P., Eichmann, T.O., Kolb, D., Grabner, G.F., Wolinski, H., Gruber, R., Hofer, P., Heier, C., Schauer, S., Rulicke, T., Hoefler, G., Schmuth, M., Elias, P.M., Lass, A., Zechner, R. and Haemmerle, G. (2017) Skin barrier development depends on CGI-58 protein expression during late-stage keratinocyte differentiation. J. Invest. Dermatol. **137**, 403–413.
164) Radner, F.P., Streith, I.E., Schoiswohl, G., Schweiger, M., Kumari, M., Eichmann, T.O., Rechberger, G., Koefeler, H.C., Eder, S., Schauer, S., Theussl, H.C., Preiss-Landl, K., Lass, A., Zimmermann, R., Hoefler, G., Zechner, R. and Haemmerle, G. (2010) Growth retardation,

impaired triacylglycerol catabolism, hepatic steatosis, and lethal skin barrier defect in mice lacking comparative gene identification-58 (CGI-58). J. Biol. Chem. **285**, 7300–7311.

165) Zhao, S., Mugabo, Y., Ballentine, G., Attane, C., Iglesias, J., Poursharifi, P., Zhang, D., Nguyen, T.A., Erb, H., Prentki, R., Peyot, M.L., Joly, E., Tobin, S., Fulton, S., Brown, J.M., Madiraju, S.R. and Prentki, M. (2016) α/β-hydrolase domain 6 deletion induces adipose browning and prevents obesity and type 2 diabetes. Cell Rep. **14**, 2872–2888.

166) Duchez, A.C., Boudreau, L.H., Naika, G.S., Bollinger, J., Belleannee, C., Cloutier, N., Laffont, B., Mendoza-Villarroel, R.E., Levesque, T., Rollet-Labelle, E., Rousseau, M., Allaeys, I., Tremblay, J.J., Poubelle, P.E., Lambeau, G., Pouliot, M., Provost, P., Soulet, D., Gelb, M.H. and Boilard, E. (2015) Platelet microparticles are internalized in neutrophils via the concerted activity of 12-lipoxygenase and secreted phospholipase A_2-IIA. Proc. Natl. Acad. Sci. U.S.A. **112**, E3564–E3573.

167) Schewe, M., Franken, P.F., Sacchetti, A., Schmitt, M., Joosten, R., Bottcher, R., van Royen, M.E., Jeammet, L., Payre, C., Scott, P.M., Webb, N.R., Gelb, M., Cormier, R.T., Lambeau, G. and Fodde, R. (2016) Secreted phospholipases A_2 are intestinal stem cell niche factors with distinct roles in homeostasis, inflammation, and cancer. Cell Stem Cell **19**, 38–51.

168) Munoz, N.M., Meliton, A.Y., Meliton, L.N., Dudek, S.M. and Leff, A.R. (2009) Secretory group V phospholipase A_2 regulates acute lung injury and neutrophilic inflammation caused by LPS in mice. Am. J. Physiol. Lung Cell. Mol. Physiol. **296**, L879–L887.

169) Bostrom, M.A., Boyanovsky, B.B., Jordan, C.T., Wadsworth, M.P., Taatjes, D.J., de Beer, F.C. and Webb, N.R. (2007) Group v secretory phospholipase A_2 promotes atherosclerosis: evidence from genetically altered mice. Arterioscler. Thromb. Vasc. Biol. **27**, 600–606.

170) Yano, T., Fujioka, D., Saito, Y., Kobayashi, T., Nakamura, T., Obata, J.E., Kawabata, K., Watanabe, K., Watanabe, Y., Mishina, H., Tamaru, S. and Kugiyama, K. (2011) Group V secretory phospholipase A_2 plays a pathogenic role in myocardial ischaemia-reperfusion injury. Cardiovasc. Res. **90**, 335–343.

171) Boyanovsky, B.B., Bailey, W., Dixon, L., Shridas, P. and Webb, N.R. (2012) Group V secretory phospholipase A_2 enhances the progression of angiotensin II-induced abdominal aortic aneurysms but confers protection against angiotensin II-induced cardiac fibrosis in apoE-deficient mice. Am. J. Pathol. **181**, 1088–1098.

172) Shridas, P., Zahoor, L., Forrest, K.J., Layne, J.D. and Webb, N.R. (2014) Group X secretory phospholipase A_2 regulates insulin secretion through a cyclooxygenase-2-dependent mechanism. J. Biol. Chem. **289**, 27410–27417.

173) Shridas, P., Bailey, W.M., Talbott, K.R., Oslund, R.C., Gelb, M.H. and Webb, N.R. (2011) Group X secretory phospholipase A_2 enhances TLR4 signaling in macrophages. J. Immunol. **187**, 482–489.

174) Ait-Oufella, H., Herbin, O., Lahoute, C., Coatrieux, C., Loyer, X., Joffre, J., Laurans, L., Ramkhelawon, B., Blanc-Brude, O., Karabina, S., Girard, C.A., Payre, C., Yamamoto, K., Binder, C.J., Murakami, M., Tedgui, A., Lambeau, G. and Mallat, Z. (2013) Group X secreted phospholipase A_2 limits the development of atherosclerosis in LDL receptor-null mice. Arterioscler. Thromb. Vasc. Biol. **33**, 466–473.

175) Zack, M., Boyanovsky, B.B., Shridas, P., Bailey, W., Forrest, K., Howatt, D.A., Gelb, M.H., de Beer, F.C., Daugherty, A. and Webb, N.R. (2011) Group X secretory phospholipase A_2 augments angiotensin II-induced inflammatory responses and abdominal aortic aneurysm formation in apoE-deficient mice. Atherosclerosis **214**, 58–64.

176) Watanabe, K., Fujioka, D., Saito, Y., Nakamura, T., Obata, J.E., Kawabata, K., Watanabe, Y., Mishina, H., Tamaru, S., Hanasaki, K. and Kugiyama, K. (2012) Group X secretory PLA_2 in neutrophils plays a pathogenic role in abdominal aortic aneurysms in mice. Am. J. Physiol. Heart Circ. Physiol. **302**, H95–H104.

177) Grall, A., Guaguere, E., Planchais, S., Grond, S., Bourrat, E., Hausser, I., Hitte, C., Le Gallo, M., Derbois, C., Kim, G.J., Lagoutte, L., Degorce-Rubiales, F., Radner, F.P., Thomas, A., Kury, S., Bensignor, E., Fontaine, J., Pin, D., Zimmermann, R., Zechner, R., Lathrop, M., Galibert, F., Andre, C. and Fischer, J. (2012) *PNPLA1* mutations cause autosomal recessive congenital ichthyosis in golden retriever dogs and humans. Nat. Genet. **44**, 140–147.

178) Fischer, J., Lefevre, C., Morava, E., Mussini, J.M., Laforet, P., Negre-Salvayre, A., Lathrop, M. and Salvayre, R. (2007) The gene encoding adipose triglyceride lipase (*PNPLA2*) is mutated in neutral lipid storage disease with myopathy. Nat. Genet. **39**, 28–30.

179) Rainier, S., Bui, M., Mark, E., Thomas, D., Tokarz, D., Ming, L., Delaney, C., Richardson, R.J., Albers, J.W., Matsunami, N., Stevens, J., Coon, H., Leppert, M. and Fink, J.K. (2008) Neuropathy target esterase gene mutations cause motor neuron disease. Am. J. Hum. Genet. **82**, 780–785.

180) Vrieze, S.I., Malone, S.M., Pankratz, N., Vaidyanathan, U., Miller, M.B., Kang, H.M., McGue, M., Abecasis, G. and Iacono, W.G. (2014) Genetic associations of nonsynonymous exonic variants with psychophysiological endophenotypes. Psychophysiology **51**, 1300–1308.

181) Falchi, M., Bataille, V., Hayward, N.K., Duffy, D.L., Bishop, J.A., Pastinen, T., Cervino, A., Zhao, Z.Z., Deloukas, P., Soranzo, N., Elder, D.E., Barrett, J.H., Martin, N.G., Bishop, D.T., Montgomery, G.W. and Spector, T.D. (2009) Genome-wide association study identifies variants at 9p21 and 22q13 associated with development of

cutaneous nevi. Nat. Genet. **41**, 915–919.
182) Koenig, W., Khuseyinova, N., Lowel, H., Trischler, G. and Meisinger, C. (2004) Lipoprotein-associated phospholipase A_2 adds to risk prediction of incident coronary events by C-reactive protein in apparently healthy middle-aged men from the general population: results from the 14-year follow-up of a large cohort from southern Germany. Circulation **110**, 1903–1908.
183) Wootton, P.T., Drenos, F., Cooper, J.A., Thompson, S.R., Stephens, J.W., Hurt-Camejo, E., Wiklund, O., Humphries, S.E. and Talmud, P.J. (2006) Tagging-SNP haplotype analysis of the secretory PLA_2IIa gene *PLA2G2A* shows strong association with serum levels of $sPLA_2$IIa: results from the UDACS study. Hum. Mol. Genet. **15**, 355–361.
184) Leung, S.Y., Chen, X., Chu, K.M., Yuen, S.T., Mathy, J., Ji, J., Chan, A.S., Li, R., Law, S., Troyanskaya, O.G., Tu, I.P., Wong, J., So, S., Botstein, D. and Brown, P.O. (2002) Phospholipase A_2 group IIA expression in gastric adenocarcinoma is associated with prolonged survival and less frequent metastasis. Proc. Natl. Acad. Sci. U.S.A. **99**, 16203–16208.
185) Takabatake, N., Sata, M., Inoue, S., Shibata, Y., Abe, S., Wada, T., Machiya, J., Ji, G., Matsuura, T., Takeishi, Y., Muramatsu, M. and Kubota, I. (2005) A novel polymorphism in secretory phospholipase A_2-IID is associated with body weight loss in chronic obstructive pulmonary disease. Am. J. Respir. Crit. Care Med. **172**, 1097–1104.
186) McGovern, D.P., Gardet, A., Torkvist, L., Goyette, P., Essers, J., Taylor, K.D., Neale, B.M., Ong, R.T., Lagace, C., Li, C., Green, T., Stevens, C.R., Beauchamp, C., Fleshner, P.R., Carlson, M., D'Amato, M., Halfvarson, J., Hibberd, M.L., Lordal, M., Padyukov, L., Andriulli, A., Colombo, E., Latiano, A., Palmieri, O., Bernard, E.J., Deslandres, C., Hommes, D.W., de Jong, D.J., Stokkers, P.C., Weersma, R.K., Consortium, N.I.G., Sharma, Y., Silverberg, M.S., Cho, J.H., Wu, J., Roeder, K., Brant, S.R., Schumm, L.P., Duerr, R.H., Dubinsky, M.C., Glazer, N.L., Haritunians, T., Ippoliti, A., Melmed, G.Y., Siscovick, D.S., Vasiliauskas, E.A., Targan, S.R., Annese, V., Wijmenga, C., Pettersson, S., Rotter, J.I., Xavier, R.J., Daly, M.J., Rioux, J.D. and Seielstad, M. (2010) Genome-wide association identifies multiple ulcerative colitis susceptibility loci. Nat. Genet. **42**, 332–337.
187) Kazama, S., Kitayama, J., Hiyoshi, M., Taketomi, Y., Murakami, M., Nishikawa, T., Tanaka, T., Tanaka, J., Kiyomatsu, T., Kawai, K., Hata, K., Yamaguchi, H., Nozawa, H., Ishihara, S., Sunami, E. and Watanabe, T. (2015) Phospholipase A_2 group III and group X have opposing associations with prognosis in colorectal cancer. Anticancer Res. **35**, 2983–2990.
188) Hoeft, B., Linseisen, J., Beckmann, L., Muller-Decker, K., Canzian, F., Husing, A., Kaaks, R., Vogel, U., Jakobsen, M.U., Overvad, K., Hansen, R.D., Knuppel, S., Boeing, H., Trichopoulou, A., Koumantaki, Y., Trichopoulos, D., Berrino, F., Palli, D., Panico, S., Tumino, R., Bueno-de-Mesquita, H.B., van Duijnhoven, F.J., van Gils, C.H., Peeters, P.H., Dumeaux, V., Lund, E., Huerta Castano, J.M., Munoz, X., Rodriguez, L., Barricarte, A., Manjer, J., Jirstrom, K., Van Guelpen, B., Hallmans, G., Spencer, E.A., Crowe, F.L., Khaw, K.T., Wareham, N., Morois, S., Boutron-Ruault, M.C., Clavel-Chapelon, F., Chajes, V., Jenab, M., Boffetta, P., Vineis, P., Mouw, T., Norat, T., Riboli, E. and Nieters, A. (2010) Polymorphisms in fatty-acid-metabolism-related genes are associated with colorectal cancer risk. Carcinogenesis **31**, 466–472.
189) Martinez-Garcia, A., Sastre, I., Recuero, M., Aldudo, J., Vilella, E., Mateo, I., Sanchez-Juan, P., Vargas, T., Carro, E., Bermejo-Pareja, F., Rodriguez-Rodriguez, E., Combarros, O., Rosich-Estrago, M., Frank, A., Valdivieso, F. and Bullido, M.J. (2010) PLA2G3, a gene involved in oxidative stress induced death, is associated with Alzheimer's disease. J. Alzheimers Dis. **22**, 1181–1187.
190) Wootton, P.T., Arora, N.L., Drenos, F., Thompson, S.R., Cooper, J.A., Stephens, J.W., Hurel, S.J., Hurt-Camejo, E., Wiklund, O., Humphries, S.E. and Talmud, P.J. (2007) Tagging SNP haplotype analysis of the secretory PLA_2-V gene, PLA2G5, shows strong association with LDL and oxLDL levels, suggesting functional distinction from $sPLA_2$-IIA: results from the UDACS study. Hum. Mol. Genet. **16**, 1437–1444.
191) Sergouniotis, P.I., Davidson, A.E., Mackay, D.S., Lenassi, E., Li, Z., Robson, A.G., Yang, X., Kam, J.H., Isaacs, T.W., Holder, G.E., Jeffery, G., Beck, J.A., Moore, A.T., Plagnol, V. and Webster, A.R. (2011) Biallelic mutations in PLA2G5, encoding group V phospholipase A_2, cause benign fleck retina. Am. J. Hum. Genet. **89**, 782–791.

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Profile

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