thematic review series

Thematic Review Series: Phospholipases: Central Role in Lipid Signaling and Disease

A new era of secreted phospholipase A_2

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Abstract Among more than 30 members of the phospholipase A_2 (PLA_2) superfamily, secreted PLA_2 ($sPLA_2$) enzymes represent the largest family, being Ca^{2+}-dependent low-molecular-weight enzymes with a His-Asp catalytic dyad. Individual $sPLA_2$s exhibit unique tissue and cellular distributions and enzymatic properties, suggesting their distinct biological roles. Recent studies using transgenic and knockout mice for nearly a full set of $sPLA_2$ subtypes, in combination with sophisticated lipidomics as well as biochemical and cell biological studies, have revealed distinct contributions of individual $sPLA_2$s to various pathophysiological events, including production of pro- and anti-inflammatory lipid mediators, regulation of membrane remodeling, degradation of foreign phospholipids in microbes or food, or modification of extracellular noncellular lipid components. In this review, we highlight the current understanding of the in vivo functions of $sPLA_2$s and the underlying lipid pathways as revealed by a series of studies over the last decade.— Murakami, M., H. Sato, Y. Miki, K. Yamamoto, and Y. Taketomi. **A new era of secreted phospholipase A_2. *J. Lipid Res.* 2015.** 56: **1248–1261.**

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More than one third of the phospholipase A_2 (PLA_2) enzymes belong to the secreted PLA_2 ($sPLA_2$) family, which contains 10 catalytically active isoforms (IB, IIA, IIC, IID, IIE, IIF, III, V, X, and XIIA) and one inactive isoform (XIIB) in mammals (1–4). Individual $sPLA_2$s exhibit unique tissue and cellular distributions and substrate selectivity, suggesting their distinct biological roles. Because $sPLA_2$s are secreted and require millimolar Ca^{2+} for their catalytic action, they principally target phospholipids in the extracellular space. Individual $sPLA_2$s participate in diverse biological events through generation of a variety of lipid mediators, promotion of membrane remodeling, modification of extracellular noncellular lipid components such as surfactant, microparticles and lipoproteins, or degradation of foreign phospholipids in microbes and dietary components in response to given microenvironmental cues. The biological effects of $sPLA_2$s may also be driven or counter-regulated by binding to soluble and membrane-bound M-type $sPLA_2$ receptor (PLA2R1). Therefore, the phenotypes displayed in $sPLA_2$ gene-manipulated mice may not rely merely on the changes in lipid mediator signaling (more particularly eicosanoid signaling), but may also involve one or a combination of the above possibilities. Here, we overview the latest knowledge regarding the pathophysiological roles of individual $sPLA_2$s as revealed by studies using gene-manipulated mice over the past decade, focusing particularly on their target substrates and products in vivo. The classification and biochemical properties of $sPLA_2$s have also been detailed in other elegant reviews (1–6).

GENERAL ASPECTS

Conventional $sPLA_2$s (group I/II/V/X) are closely related low-molecular-weight enzymes with a highly conserved Ca^{2+}-binding loop and a His/Asp catalytic dyad as well as conserved disulfide bonds, while atypical $sPLA_2$s (group III and XII) are each classified into distinct classes (**Fig. 1**). Of these, $sPLA_2$-IB and -IIA are two prototypic $sPLA_2$s that were originally identified by classical protein purification from pancreas and inflamed sites, respectively

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Abbreviations: AA, arachidonic acid; DC, dendritic cell; DPA, docosapentaenoic acid; LPC, lysophosphatidylcholine; LPCAT1, lysophosphatidylcholine acyltransferase 1; LPE, lysophosphatidylethanolamine; L-PGDS, lipocalin-type prostaglandin D_2 synthase; LPS, lipopolysaccharide; PC, phosphatidylcholine; PE, phosphatidylethanolamine; PG, phosphatidylglycerol; PGD_2, prostaglandin D_2; PGE_2, prostaglandin E_2; PS, phosphatidylserine; PLA_2, phospholipase A_2; $cPLA_2\alpha$, cytosolic phospholipase $A_2\alpha$; $sPLA_2$, secreted phospholipase A_2; PLA2R1, M-type secreted phospholipase A_2 receptor.

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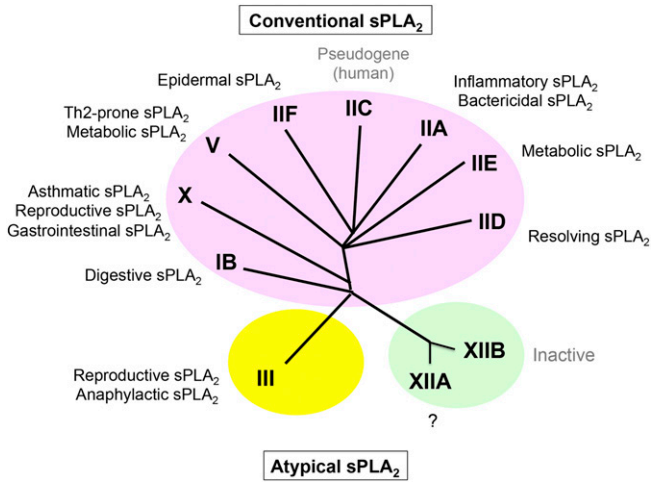

Fig. 1. A phylogenetic tree of the $sPLA_2$ family and the functions of individual $sPLA_2$s as revealed by studies using gene-manipulated mice. Several examples for the functions of individual $sPLA_2$s, in which underlying lipid metabolisms have been clarified (see text), are illustrated on the phylogenetic tree. The overall functions of $sPLA_2$s reported so far are summarized in Table 1. Although $sPLA_2$-XIIB, which is catalytically inactive, has been implicated in steatohepatitis, the mechanistic action is unknown.

(7–10). Structurally, $sPLA_2$-IB and -IIA are similar to snake venom group I and II $sPLA_2$s, respectively. Among the conventional $sPLA_2$s, $sPLA_2$-IB is evolutionally the oldest $sPLA_2$ isoform in the animal kingdom because three genes encoding IB-like $sPLA_2$s are present in nematode (*Caenorhabditis elegans*), whereas group II, V, and X $sPLA_2$s exist only in vertebrates (3). $sPLA_2$-V does not possess the key features of group I and II $sPLA_2$s, yet it is often classified into the group II subfamily of $sPLA_2$s because its gene is mapped to the group II $sPLA_2$ cluster locus (11, 12). $sPLA_2$-X has both group I- and group II-like structural features, suggesting that it emerged during the diversification from group I to II $sPLA_2$s (13). $sPLA_2$-III is an atypical $sPLA_2$ that is more similar to bee venom group III $sPLA_2$ than to other mammalian $sPLA_2$s (14). Another atypical $sPLA_2$-XII subfamily, XIIA and XIIB, has very unique structural and functional features (15, 16), and the preservation of $sPLA_2$-XII members from bacteria to human indicates that they emerged early in evolution prior to *Eubacteria* (17). Currently known $sPLA_2$ inhibitors can inhibit conventional $sPLA_2$s to various degrees, yet an agent that specifically inhibits $sPLA_2$-III or -XIIA has not yet become available. Otoconin-90/95, which has two $sPLA_2$-IB-like domains, can also be classified into the $sPLA_2$ family, yet we do not describe it in detail here because it is a structural protein of the inner ear and is unrelated to phospholipid metabolism (18, 19).

Biochemical analyses using pure $sPLA_2$s have shown that individual $sPLA_2$s have distinct substrate selectivity in terms of the polar head groups or *sn*-2 fatty acids of phospholipids. For instance, $sPLA_2$-X is very active on phosphatidylcholine (PC), while $sPLA_2$-IIA has much higher affinity for phosphatidylethanolamine (PE) or phosphatidylserine (PS) than for PC, and this substrate selectivity is partly attributable to their crystal structures (20, 21). With regard to *sn*-2 fatty acid specificity, $sPLA_2$-IB, -IIA, and -III do not discriminate fatty acid species, $sPLA_2$-V tends to prefer those with a lower degree of unsaturation such as oleic acid, and $sPLA_2$-X tends to prefer PUFAs including arachidonic acid (AA) and DHA (22–26). It should be noted that the enzyme activity is influenced by the assay conditions employed, such as the composition of the substrate phospholipids (pure phospholipid vesicles or mixed micelles comprising multiple phospholipid species), the concentrations of the $sPLA_2$s, presence of detergents, pH, and so on. Hence, the enzymatic properties of individual $sPLA_2$s determined in different studies are not entirely identical. The use of excess super-physiological amounts of $sPLA_2$ in in vitro experiments often masks the substrate selectivity. As membranes comprising a single phospholipid molecular species do not exist and detergent is absent under most physiological conditions, a result obtained using artificial phospholipid membranes may not reflect the true enzymatic properties of a given $sPLA_2$. An exception is $sPLA_2$-IB, for which a detergent (bile acid) is important for full enzymatic activity in the intestinal lumen (27). Ideally, the enzymatic activity of each $sPLA_2$ isoform should be evaluated at a physiologically relevant enzyme concentration and with a physiologically relevant membrane on which the enzyme acts intrinsically. Nonetheless, the overall selectivity of $sPLA_2$s for the various phospholipid head groups and for saturated versus unsaturated fatty acids has been well-depicted by several in vitro enzymatic studies, and the in vivo data using lipidomics have revealed an even more selective pattern of hydrolysis. In some aspects, the use of transgenic versus knockout mice is similar to the in vitro versus in vivo studies regarding the $sPLA_2$ selectivity toward the full diversity of phospholipids with various head groups and *sn*-2 fatty acids.

Some of the biological actions of $sPLA_2$s in vivo have been investigated using $sPLA_2$-overexpressing transgenic mice (28–38). However, the results should be interpreted with caution, as a super-physiological level of $sPLA_2$, even in tissues or cells where the enzyme is not intrinsically expressed, could result in an artificial phenotype. Nevertheless, studies using transgenic mice have yielded informative insights into some of the pathophysiological roles of $sPLA_2$s. If mice transgenic for a certain $sPLA_2$ display a particular phenotype opposite to that in knockout mice lacking the same $sPLA_2$, it can be concluded that this phenotype represents the intrinsic function of this $sPLA_2$ isoform. In cases such as this, transgenic mice are useful when searching for lipid-metabolic processes driven by a particular $sPLA_2$ in vivo, because lipid mobilization in the transgenic mice is typically prominent and easy to chase using a lipidomics approach. Another noteworthy issue is that the overall phenotypes of mice transgenic for different $sPLA_2$s are not entirely identical (28–38). If different $sPLA_2$s have similar enzymatic properties, then the output phenotypes of mice transgenic for them should be similar. However, this is not actually the case. Why do mice transgenic for different $sPLA_2$s display distinct phenotypes? The most likely explanation is that individual $sPLA_2$s have distinct enzymatic properties, acting on different phospholipid substrates and mobilizing

different lipid metabolites in vivo. Likewise, while it is undeniable that knockout mice have provided much insight into the pathophysiological role of sPLA$_2$s, there is often the potential problem of compensatory mechanisms (i.e., that one enzyme compensates the absence of a related one by increasing its expression, activity, and/or function). However, accumulating evidence obtained from knockout mice for different sPLA$_2$s suggests that it is also not the case in most situations, likely because each sPLA$_2$ displays unique substrate selectivity and tissue distribution. This point implies that sPLA$_2$s are not "functional" isozymes in vivo.

In order to comprehensively understand the specific biological roles of this enzyme family, it is important to consider as to when and where different sPLA$_2$s are expressed, which isoforms are involved in specific types of pathophysiology, and how the sPLA$_2$s exhibit their unique functions by driving specific types of lipid metabolism. In subsequent sections, we will describe the functions of individual sPLA$_2$s as revealed by studies using knockout and/or transgenic mice along with lipidomics approaches to clarify their in vivo substrates and metabolites. The roles of individual sPLA$_2$s, and the underlying lipid-metabolic pathways in which they are involved, are summarized in **Table 1**, and several examples are illustrated in Fig. 1 and **Fig. 2**.

CONVENTIONAL sPLA$_2$s

PLA2G1B/sPLA$_2$-IB

sPLA$_2$-IB is abundantly expressed in the pancreas, and to a much lesser extent in the lung and kidney. After secretion from pancreatic acinar cells into the duodenal lumen, an N-terminal heptapeptide of the inactive zymogen is cleaved by trypsin to yield an active enzyme (7, 8). Gene disruption of sPLA$_2$-IB (*Pla2g1b*$^{-/-}$) results in decreased digestion of dietary and biliary phospholipids in the gastrointestinal tract (39). Accordingly, the reduced gastrointestinal production and absorption of lysophosphatidylcholine (LPC), a causal factor for insulin resistance, confers protection against diet-induced obesity, glucose intolerance, hyperlipidemia, and atherosclerosis in *Pla2g1b*$^{-/-}$ mice (40–43). On the other hand, pancreatic acinar cell-specific *Pla2g1b*-transgenic mice develop more severe obesity and insulin resistance (28). Oral supplementation with methyl-indoxam, a pan-sPLA$_2$ inhibitor, prevents diet-induced obesity and diabetes in mice, most probably through inhibition of sPLA$_2$-IB (44). Moreover, the *PLA2G1B* gene maps to a locus for obesity susceptibility in humans (45). Thus, pharmacological inhibition of sPLA$_2$-IB, a "digestive sPLA$_2$," could be an effective oral therapeutic option for treatment of metabolic diseases.

PLA2G2A/sPLA$_2$-IIA

sPLA$_2$-IIA is the only isoform detectable in the circulation, particularly under pathological conditions. Because sPLA$_2$-IIA expression is induced by pro-inflammatory stimuli in various cells and because its levels in sera or inflammatory exudates are correlated with the severity of inflammation (9, 10, 46), it is often referred to as an "inflammatory sPLA$_2$." However, the precise role of sPLA$_2$-IIA in inflammation has remained unknown until recently, because a frameshift mutation in the *Pla2g2a* gene in C57BL/6 and 129Sv mice has prevented adequate evaluation of its functions by gene targeting (47, 48). Up to now, therefore, the in vivo functions of sPLA$_2$-IIA have been addressed mainly using transgenic mice.

The most probable physiological role of sPLA$_2$-IIA is degradation of bacterial membranes, thereby providing a first line of antimicrobial defense (49). Indeed, sPLA$_2$-IIA kills bacteria (Gram-positive in particular) at physiological concentrations (50). Bacterial membranes are rich in PE and phosphatidylglycerol (PG), whereas PC is a major phospholipid in the outer leaflet of the plasma membrane of mammalian cells. sPLA$_2$-IIA has a much higher affinity for PE and PG than PC, thus accounting for the preferential action of this enzyme on bacterial cells rather than on mammalian cells. In addition to this substrate specificity, the highly cationic nature of sPLA$_2$-IIA, which is not shared with other sPLA$_2$s, is essential for bacterial membrane hydrolysis by this enzyme (51, 52). As such, *PLA2G2A*-transgenic mice, or wild-type mice treated with recombinant sPLA$_2$-IIA, are resistant to pneumonia and sepsis following bacterial infection (31, 32, 53–55). For this reason, sPLA$_2$-IIA can be regarded as a "bactericidal sPLA$_2$." Some bacteria such as *Pseudomonas aeruginosa* and *Bacillus anthracis* have developed a resistance mechanism against sPLA$_2$-IIA by inhibiting its induction in macrophages (55, 56).

Mouse strains with natural disruption of the *Pla2g2a* gene (see above) are more sensitive to intestinal tumorigenesis (48). Transgenic transfer of the *Pla2g2a* gene into these mice reduces the incidence of intestinal polyposis (57), indicating that sPLA$_2$-IIA acts as a tumor suppressor in the gastrointestinal tract. Consistently, there is an inverse relationship between *PLA2G2A* expression and gastric cancer in humans (58), and polymorphisms in the *PLA2G2A* gene are associated with fundic gland polyposis in patients with familial adenomatous polyposis (59). Given its function as a "bactericidal sPLA$_2$," sPLA$_2$-IIA secreted from intestinal Paneth cells might control the gastrointestinal microflora, thereby preventing tumor development. In contrast, sPLA$_2$-IIA expression shows a positive correlation with several types of cancer, including prostate cancer (60–62), suggesting distinct impacts of sPLA$_2$-IIA on different types of cancer.

In a recent study, the mutated *Pla2g2a* allele in the C57BL/6 strain was backcrossed onto the BALB/c strain to produce *Pla2g2a*$^{-/-}$ BALB/c mice. These *Pla2g2a*$^{-/-}$ mice are protected from autoantibody-induced arthritis, while *PLA2G2A*-transgenic mice display more severe symptoms in the same model (63), thus providing compelling evidence for the bona fide pro-inflammatory role of sPLA$_2$-IIA. Mechanistically, sPLA$_2$-IIA targets phospholipids in microparticles, particularly in extracellular mitochondria, thereby amplifying inflammation (64). Mitochondria, which were originated from bacteria during evolution, are released from activated platelets or leukocytes to accumulate at inflamed sites (65). Hydrolysis of the mitochondrial membrane by sPLA$_2$-IIA yields inflammatory mediators

TABLE 1. $sPLA_2$-driven lipid-metabolic pathways in homeostasis and diseases

$sPLA_2$s	Distributions	Target Membranes	Products	Mechanistic Insights	Homeostasis and Diseases	References
IB	Pancreatic acinar cells	Dietary and biliary PC in the gastrointestinal tract	LPC	Phospholipid digestion in the gastrointestinal lumen	Metabolic disorders, atherosclerosis	39–43
IIA	Platelets, leukocytes, Paneth cells	Bacterial membranes	Lipid mediator-independent	Killing of Gram-positive bacteria	Host defense	31, 32, 53–55
		Extracellular mitochondria	Eicosanoids	Amplification of inflammation	Arthritis	63, 64
		Unknown	Unknown	Regulation of intestinal microflora?	Anti-colon cancer	57
IID	Lymph tissue DCs	DHA-containing PE	DHA and resolvin D1	Resolution of Th1 immunity	Anti-contact dermatitis	70
IIE	Hypertrophic adipocytes	PE and PS in lipoproteins	Lipid mediator-independent	Fat deposition in adipose tissue and liver	Obesity	74
IIF	Keratinocytes	Unknown	Unknown	Unknown	Epidermal barrier	79
V	Bronchial epithelial cells	Surfactant dipalmitoyl-PC	Lipid mediator-independent	Surfactant degradation	Airway injury	34
	Macrophages, DCs	Unknown	Unknown	M2 macrophage polarization and Th2 immunity	Asthma	84–86, 92–95
			LPE	Phagocytosis of microorganisms	Host defense	96, 97
			LPE?	Phagocytosis of immune complexes	Anti-arthritis	63
	Hematopoietic cells	Unknown	Unknown	Atherosclerotic plaque formation	Atherosclerosis	99
	Cardiomyocytes	Unknown	Eicosanoids (indirect?)	Apoptosis of injured myocardial cells	Myocardial infarction	101
	Aorta	Unknown	Unknown	Aortic inflammation	Aneurysm	102
	Hypertrophic adipocytes	PC in LDL	Oleic and linoleic acids	Reduced adipose tissue inflammation by unsaturated fatty acids	Anti-obesity	74
X	Airway epithelium	Infiltrating eosinophils, airway epithelial cells	Eicosanoids (indirect?)	Airway inflammation	Asthma, influenza infection	94, 112, 113, 116
	Macrophages?	Unknown	PUFAs?	Enhanced lipid accumulation and TLR4 signaling in macrophages	Macrophage function	127
	Adrenal glands	Unknown	PUFAs?	Reduced corticosteroid synthesis by downregulating adrenal steroidogenic acute regulatory protein	Hypercorticosteronemia	122
	Dorsal root ganglia	Unknown	LPC?	Neuritogenesis and pain transmission	Pain	121
	Hematopoietic cells	Unknown	Unknown	Reduced Th1 immunity and atherosclerotic plaque formation	Anti-atherosclerosis	124
	Neutrophils	Unknown	Eicosanoids (indirect?)	Tissue damage by neutrophils	Aneurysm, myocardial infarction	118–120
	Pancreatic β cells	Unknown	PGE_2	Suppression of insulin secretion	Diabetes	123
	Gut epithelium	Dietary and biliary PC in the gastrointestinal tract	LPC	Phospholipid digestion in the gastrointestinal lumen	Adiposity	121
	Adipocytes?	Unknown	PUFAs?	Repression of adipogenesis by inhibiting liver X receptor activation	Anti-obesity	128
	Sperm acrosome	PC in sperm membrane	LPC	Boosting acrosome reaction	Male fertility	132
	Hair follicles	Unknown	Unknown	Hair homeostasis	Alopecia	36
III	Mast cells	Adjacent fibroblasts	PGD_2	Promotion of mast cell maturation	Anaphylaxis	134
	Epididymal epithelium	PC in sperm membrane	Lipid mediator-independent	Sperm maturation by membrane phospholipid remodeling	Male fertility	135
XIIB	Hepatocytes	Unknown	Unknown	Hepatic secretion of VLDL	Steatohepatitis	145

Distributions, target membranes and products, underlying mechanisms, and related diseases for $sPLA_2$s are summarized. Their key substrates and products have been identified in several, but not in many other, cases.

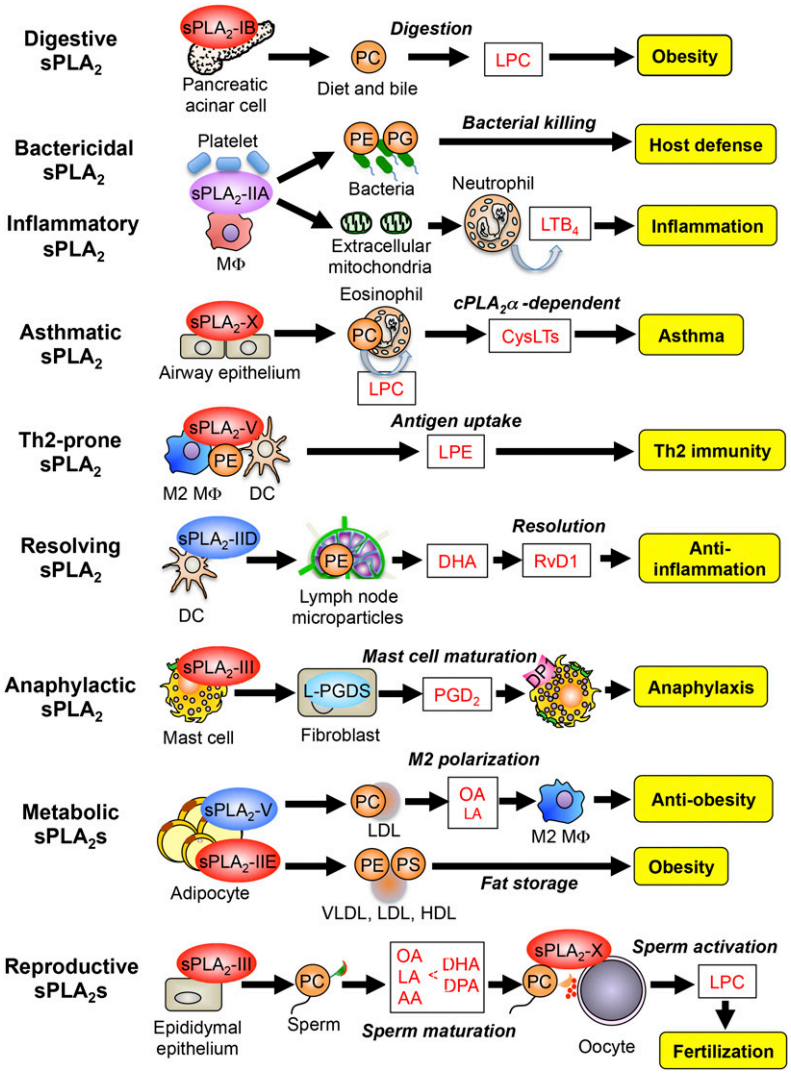

Fig. 2. Examples of the $sPLA_2$-driven lipid pathways. Individual $sPLA_2$s are involved in distinct biological processes or diseases through driving unique lipid pathways that involve or do not depend on lipid mediators. In all cases, $sPLA_2$s act on extracellular phospholipids (e.g., adjacent cells, lipoproteins, microparticles, diet, and bacteria membranes) after secretion. For details, please see the text. RvD1, resolvin D1; OA, oleic acid; LA, linoleic acid.

including eicosanoids and lysophospholipids as well as mitochondrial DNA as a danger-associated molecular pattern, which promotes leukocyte activation. Moreover, $sPLA_2$-IIA-targeted extracellular mitochondria interact with neutrophils, triggering adhesion of these cells to the vascular wall. This breakthrough finding explains a long-sought mechanism for the function of $sPLA_2$-IIA as an "inflammatory $sPLA_2$." Thus, $sPLA_2$-IIA is primarily involved in host defense by both killing bacteria and alarming the innate immunity response, and over-amplification of the response can lead to excessive inflammation. In the latter case, $sPLA_2$-IIA can be viewed as a "double-edged sword."

Transgenic overexpression of $sPLA_2$-IIA results in skin abnormalities manifested by hair loss and epidermal hyperplasia (29), and by increased carcinogen-induced skin cancer (33). Importantly, $sPLA_2$-IIA has long been implicated in atherosclerosis as a potential causal factor or as a biomarker in many studies, which are summarized in previous reviews (1–6). For instance, in line with clinical evidence that *PLA2G2A* gene polymorphisms are associated with atherosclerosis (66) and that serum $sPLA_2$-IIA levels show a positive correlation with cardiovascular diseases (67), *PLA2G2A*-transgenic mice develop more advanced atherosclerotic lesions (30, 68). However, conclusive evidence for the offensive roles of $sPLA_2$-IIA in skin and atherosclerosis will await future studies using *Pla2g2a*$^{-/-}$ mice on the proper genetic background.

PLA2G2D/$sPLA_2$-IID

$sPLA_2$-IID shows the closest structural relationship to $sPLA_2$-IIA (69). This isoform is expressed preferentially in dendritic cells (DCs) in secondary lymphoid organs such as the spleen and lymph nodes of mice and humans (70), suggesting its regulatory role in adaptive immunity. In a model of Th1-dependent contact hypersensitivity, resolution of inflammation is compromised in the skin and lymph nodes of *Pla2g2d*$^{-/-}$ mice (70). $sPLA_2$-IID in regional lymph nodes mobilizes a pool of ω3 PUFAs that are metabolized to pro-resolving lipid mediators such as DHA-derived resolvin D1, which suppresses Th1 cytokine production and DC activation. $sPLA_2$-IID preferentially hydrolyzes DHA-containing PE in lymph node membranes (possibly in microparticles). Consistent with its anti-inflammatory role, $sPLA_2$-IID expression in DCs is down-regulated after cell activation. Furthermore, administration of $sPLA_2$-IID-Fc protein attenuates autoimmune diseases

in mice (71). Thus, sPLA$_2$-IID is a "resolving sPLA$_2$" that ameliorates inflammation by mobilizing DHA-derived pro-resolving lipid mediators. In humans, a *PLA2G2D* polymorphism is associated with body weight loss in chronic obstructive pulmonary disease (72).

PLA2G2E/sPLA$_2$-IIE

Like sPLA$_2$-IID, sPLA$_2$-IIE is structurally most homologous to sPLA$_2$-IIA (73). Expression of sPLA$_2$-IIE is markedly induced in adipocytes after high-fat feeding in vivo and during adipogenesis in vitro. *Pla2g2e*$^{-/-}$ mice are modestly protected from diet-induced obesity, fatty liver, and hyperlipidemia (74). Mechanistically, sPLA$_2$-IIE hydrolyzes minor lipoprotein phospholipids, PE, and PS, with no apparent fatty acid selectivity. As such, sPLA$_2$-IIE alters lipid composition in lipoproteins, thereby affecting fat accumulation in adipose tissue and liver. Thus, sPLA$_2$-IIE is a "metabolic sPLA$_2$" that regulates systemic metabolic states by modifying lipoprotein phospholipids. However, expression of sPLA$_2$-IIE in human adipose tissue is very low, revealing a species difference. In humans, a polymorphism in the *PLA2G2E* gene is associated with ulcerative colitis (75).

PLA2G2C/sPLA$_2$-IIC and PLA2G2F/sPLA$_2$-IIF

sPLA$_2$-IIC and -IIF have structural characteristics of group II sPLA$_2$s, but possess an extra sequence in the middle and C-terminal regions, respectively (73, 76). A cell biological study using *Pla2g2c* knockdown has shown that sPLA$_2$-IIC is upregulated in hepatitis B-infected mouse hepatocytes to produce lysophosphatidylethanolamine (LPE), which is then presented to CD1d on natural killer T cells, leading to propagation of an anti-virus immune response (77). sPLA$_2$-IIC is also expressed in meiotic cells in rodent testis (78). However, as sPLA$_2$-IIC is a pseudogene in humans (12), analysis of *Pla2g2c*$^{-/-}$ mice has not been performed.

sPLA$_2$-IIF is abundantly expressed in the suprabasal epidermis (79, 80). Gene disruption of sPLA$_2$-IIF (*Pla2g2f*$^{-/-}$) has been reported to impair the acidification of the stratum corneum and delay recovery of the skin barrier after tape-stripping (79), although a mechanistic insight is currently obscure and it should be confirmed or expanded in other ongoing studies.

PLA2G5/sPLA$_2$-V

Because sPLA$_2$-V is able to hydrolyze PC more efficiently than is sPLA$_2$-IIA (81), most investigators in this research field have focused on the potential role of this enzyme in inflammation in the context of AA metabolism. It should be noted, however, that sPLA$_2$-V releases fatty acids with a low degree of unsaturation, such as palmitic, oleic, and linoleic acids, in preference to AA from cellular membranes, lipoproteins, and even pure phospholipid vesicles (22, 23, 25, 26). Therefore, the possibility that sPLA$_2$-V mobilizes lipid metabolites other than AA-derived eicosanoids should be taken into consideration to explain the biological actions of this enzyme.

Zymosan-induced peritonitis or lipopolysaccharide (LPS)-induced air pouch inflammation is partially ameliorated in mice lacking sPLA$_2$-V (*Pla2g5*$^{-/-}$) (82, 83). sPLA$_2$-V is expressed in bronchial epithelial cells and alveolar macrophages, and *Pla2g5*$^{-/-}$ mice are protected from airway disorders such as antigen-induced asthma and LPS- or ventilator-induced alveolar injury (84–86). These studies lend support to the offensive roles of sPLA$_2$-V, yet the underlying mechanisms remain uncertain. Although these phenotypes in *Pla2g5*$^{-/-}$ mice are often accompanied by reduced levels of eicosanoids, it is unclear whether sPLA$_2$-V indeed drives AA metabolism by itself in vivo because of its fatty acid selectivity as noted above. Considering that the inflammatory responses are often accompanied by activation of cytosolic PLA$_2$α (cPLA$_2$α), a major AA-releasing PLA$_2$ (87), the observed alterations in eicosanoid levels in *Pla2g5*$^{-/-}$ mice might merely reflect the disease-associated changes in cPLA$_2$α activation, rather than hydrolytic liberation of AA by sPLA$_2$-V. In relation to this, there is evidence suggesting that sPLA$_2$-V regulates cPLA$_2$α phosphorylation (88, 89). Moreover, transgenic overexpression of sPLA$_2$-V leads to respiratory distress and neonatal death with no or only a modest increase in pulmonary eicosanoid levels (34). This transgenic phenotype is attributable to aberrant hydrolysis of surfactant phospholipids (dipalmitoyl-PC) and is apparently eicosanoid-independent.

Although sPLA$_2$-V was previously thought to be upregulated by pro-inflammatory stimuli (as in the case of sPLA$_2$-IIA) (90, 91), it has recently become obvious that its expression is induced by the Th2 cytokines, IL-4 and IL-13, much more potently than by pro-inflammatory stimuli including LPS, zymosan, and Th1 cytokines (74, 92, 93). Indeed, sPLA$_2$-V is expressed in IL-4-driven M2 macrophages and Th2 cells, which facilitate Th2-type immunity while attenuating Th1- or Th17-type immunity. Notably, Th2 responses such as IL-4 expression and IgE production are reduced in *Pla2g5*$^{-/-}$ mice (74, 92, 94), which accounts for the reduced allergic response in the absence of sPLA$_2$-V (84, 94, 95). In this regard, sPLA$_2$-V can be referred to as a "Th2-prone sPLA$_2$."

Thus, researchers should consider a bi-faceted action for sPLA$_2$-V, which could play both pro- and anti-inflammatory ("Th2-prone") roles depending on conditions, cell types, and species. In the process of Th2-dependent asthma, sPLA$_2$-V appears to function in antigen-presenting cells to regulate antigen processing and thereby the Th2 response, as well as in airway epithelial cells to promote airway injury that may involve surfactant degradation (34, 92, 94, 95). In contrast, *Pla2g5*$^{-/-}$ mice are more susceptible to *Candida albicans* or *Escherichia coli* infection (Th1 immunity) and arthritis (Th17 immunity) accompanied by reduced clearance of harmful materials (microorganisms and immune complex, respectively) by macrophages (63, 96, 97). As M2 macrophages have greater phagocytic activity, the reduced phagocytosis in *Pla2g5*$^{-/-}$ macrophages could also be partly explained by the ability of sPLA$_2$-V to promote M2 macrophage polarization in Th2 immunity and therefore to counteract Th1/Th17 immunity. Alternatively, sPLA$_2$-V may produce a certain lipid metabolite that directly regulates macrophage phagocytosis. In fact, it has recently been reported that IL-4-induced sPLA$_2$-V promotes phagocytosis in human macrophages

through production of LPE, which fully restores defective phagocytosis of zymosan and bacteria in sPLA$_2$-V-knockdown cells (93).

Because hydrolysis of phospholipids in LDL by sPLA$_2$-V is capable of promoting foam cell formation by macrophages in vitro (98), sPLA$_2$-V (and several other sPLA$_2$s) has currently been implicated in the development of atherosclerosis and related cardiovascular disorders. However, the roles of sPLA$_2$-V in cardiovascular diseases, particularly in the context of lipoprotein metabolism, are controversial. *Ldlr*$^{-/-}$ mice given transplants of *Pla2g5*$^{-/-}$ bone marrow cells are mildly protected from atherosclerosis (99); yet neither the plaque formation nor plasma LDL levels are affected by global *Pla2g5* deficiency on the *Apoe*$^{-/-}$ background (100). *Pla2g5* ablation attenuates myocardial infarction (101), while it worsens angiotensin II-induced cardiac fibrosis (102). Moreover, it has been reported that varespladib, a sPLA$_2$ inhibitor that broadly inhibits conventional sPLA$_2$s, failed to show efficacy in a phase III clinical trial for cardiovascular diseases (103). Thus, it appears that sPLA$_2$-V is not a major contributor to atherosclerosis and associated diseases, even though it may promote these diseases in certain situations. Rather, it has recently been clarified that LDL phospholipid hydrolysis by sPLA$_2$-V is associated with obesity-related metabolic syndrome.

In obesity, sPLA$_2$-V is induced in hypertrophic adipocytes (74). When fed a high-fat diet, *Pla2g5*$^{-/-}$ mice display hyperlipidemia with higher plasma levels of lipid-rich LDL and increased obesity, fatty liver, and insulin resistance. sPLA$_2$-V plays a protective role in metabolic disorders by hydrolyzing and thereby normalizing PC in LDL and by tipping the immune balance toward an Th2/M2 state that counteracts adipose tissue inflammation. Mechanistically, sPLA$_2$-V-driven oleic and linoleic acids from PC in LDL dampen M1 macrophage polarization by saturated fatty acids (e.g., palmitic acid), probably through attenuation of endoplasmic reticulum stress. Together, these studies have underscored the physiological relevance of lipoprotein hydrolysis by sPLA$_2$s, highlighted two adipocyte-driven "metabolic sPLA$_2$s" (sPLA$_2$-IIE and -V) as integrated regulators of immune and metabolic responses, and brought about a paradigm shift toward a better understanding of the roles of the sPLA$_2$ family as metabolic coordinators (74).

In humans, *PLA2G5* gene polymorphisms are correlated with LDL levels in subjects with type 2 diabetes (104). In vitro sPLA$_2$-V susceptibility of LDL from patients with type 2 diabetes is greater than that of LDL from healthy controls (105). Moreover, *PLA2G5* expression in human visceral adipose tissue inversely correlates with plasma LDL levels (74). These results imply a human relevance for the metabolic role of sPLA$_2$-V. Additionally, biallelic mutations in the *PLA2G5* gene cause benign fleck retina (106). Loss of LPC acyltransferase 1 (LPCAT1) also causes retinal degeneration (107), suggesting a potential link between sPLA$_2$-V and LPCAT1 in PC metabolism for retina homeostasis.

PLA2G10/sPLA$_2$-X

As in the case of sPLA$_2$-IB, sPLA$_2$-X is synthesized as a zymogen, and removal of an N-terminal propeptide produces an active mature enzyme (13). This processing occurs either before secretion intracellularly by furin-like convertase or after secretion extracellularly (108, 109). Among the sPLA$_2$s, sPLA$_2$-X has the highest affinity for PC and thus exhibits the most potent ability to hydrolyze plasma membrane phospholipids in intact cells (110, 111). Because of this property, many investigators have speculated that sPLA$_2$-X plays a pro-inflammatory role, although conflicting evidence also exists (see below).

Mice lacking sPLA$_2$-X (*Pla2g10*$^{-/-}$) are refractory to antigen-induced asthma, with marked reductions in infiltration of eosinophils, hyperplasia of goblet cells, thickening of the smooth muscle layer, and levels of Th2 cytokines and eicosanoids (112). The attenuated asthmatic responses in *Pla2g10*$^{-/-}$ mice are restored by knock-in of human sPLA$_2$-X, and treatment of the knock-in mice with an inhibitor specific for human sPLA$_2$-X suppresses airway inflammation (113). Mechanistically, sPLA$_2$-X secreted from the airway epithelium may act on infiltrating eosinophils to augment leukotriene production in a process involving LPC-dependent activation of cPLA$_2\alpha$ (114). In addition, sPLA$_2$-X expression is increased during in vitro epithelial differentiation and directly participates in AA release by epithelial cells (115). *Pla2g10*$^{-/-}$ mice are also partially protected from the early phase of lung inflammation in a model of pandemic influenza infection (116), further underlining the pro-inflammatory role of this enzyme in the airway. Moreover, sPLA$_2$-X is one of the major sPLA$_2$ isoforms detected in the airway of patients with asthma (117), thus directing attention to sPLA$_2$-X, an "asthmatic sPLA$_2$," as a novel therapeutic target for asthma. Unlike sPLA$_2$-V, however, sPLA$_2$-X does not influence the Th2 response itself, because antigen-sensitized *Pla2g10*$^{-/-}$ and wild-type mice have similar IgE and IL-4 levels (94).

Pla2g10$^{-/-}$ mice are also protected from myocardial infarction or aneurysm (118–120), show a reduced inflammatory pain (121), have an increased adrenal steroidogenesis (122), and exhibit alteration in insulin secretion by pancreatic β cells, perhaps as a result of reduced prostaglandin E_2 (PGE_2) synthesis (123). However, several of the phenotypes reported for *Pla2g10*$^{-/-}$ mice are controversial. Although sPLA$_2$-X (like sPLA$_2$-V) has been implicated in atherosclerosis, different groups have reported opposite (exacerbated or attenuated) atherosclerotic phenotypes in *Pla2g10*$^{-/-}$ mice (119, 124). In humans, polymorphisms in the *PLA2G10* gene are linked to a decreased risk of recurrent cardiovascular events (125), or not associated with plasma sPLA$_2$ activity or with coronary heart disease risk (126). Additionally, in different studies, *Pla2g10*$^{-/-}$ mice display altered or unaltered macrophage functions (127) or increased or decreased adiposity (121, 128). Although some of these studies were performed under the assumption that sPLA$_2$-X is expressed in macrophages or adipocytes, our own investigations have shown that its expression in these cells is low or almost undetectable. Rather, sPLA$_2$-X might be expressed in a limited subset of these cells or supplied from proximal or even distal cells in a paracrine manner. As sPLA$_2$-X is abundantly expressed in the gut epithelium (a "gastrointestinal sPLA$_2$"), it is likely that the decreased digestion and

absorption of dietary and biliary phospholipids are eventually linked to the reduced adiposity in *Pla2g10*$^{-/-}$ mice (121), a situation similar to that in *Pla2g1b*$^{-/-}$ mice (see above). Alternatively, the intestinal expression of sPLA$_2$-X might alter the microbiota, which could secondarily influence both immune and metabolic balances (129–131). This might account for some of the discrepancies observed in *Pla2g10*$^{-/-}$ mice maintained in different facilities. Another feature of note is that sPLA$_2$-X is able to release ω3 PUFAs, such as DHA, in addition to ω6 AA (26, 37). Hence, when assessing the biological roles of sPLA$_2$-X, researchers should consider the balance between ω6 and ω3 PUFA metabolism, rather than focusing only on AA metabolism.

In addition to the gastrointestinal tract, sPLA$_2$-X is abundantly expressed in the testis, where it is stored in acrosomes in the head of sperm cells (132). sPLA$_2$-X is released from activated sperm cells during the acrosome reaction. *Pla2g10*$^{-/-}$ spermatozoa display a poorer acrosome reaction and lower fertility, despite showing normal maturation and motility (121, 132). Thus, sPLA$_2$-X, a "reproductive sPLA$_2$," plays a specific role in sperm activation, boosting the acrosome reaction probably through production of some lipid products from sperm membranes in a paracrine or autocrine manner. LPC is a candidate product responsible for the action of sPLA$_2$-X, because it can partially restore the defective fertilization of wild-type sperm treated with anti-sPLA$_2$-X antibody (132).

Lastly, a striking skin phenotype characterized by alopecia in *Pla2g10*-transgenic mice points to a unique role of sPLA$_2$-X in hair homeostasis (36). Although the coat hairs of *Pla2g10*$^{-/-}$ mice appear grossly normal, they have ultrastructural abnormalities including a hypoplasic outer root sheath and reduced melanin granules in their hair follicles. However, considering that the expression of endogenous sPLA$_2$-X in mouse skin is very low, it is possible that the transgenic overexpression of sPLA$_2$-X might have mimicked the intrinsic action of a specific skin-resident sPLA$_2$ (e.g., sPLA$_2$-IIF).

ATYPICAL sPLA$_2$s

PLA2G3/sPLA$_2$-III

sPLA$_2$-III, an atypical sPLA$_2$, has a central sPLA$_2$ domain with a typical group III feature that is flanked by unique N- and C-terminal domains (14). The N- and C-terminal domains are removed to give rise to a mature sPLA$_2$ domain-only form (133). Transgenic overexpression of sPLA$_2$-III in *Apoe*$^{-/-}$ mice results in increased atherosclerosis due to accelerated LDL hydrolysis and increased thromboxane A$_2$ synthesis (37). These mice also develop systemic inflammation as they age due to increased eicosanoid formation (38). Thus, beyond the overexpression strategy, sPLA$_2$-III has pro-inflammatory potential.

Microenvironmental alterations in mast cell phenotypes affect susceptibility to allergy, yet the mechanisms underlying the proper maturation of mast cells toward an allergy-sensitive phenotype have been poorly understood. sPLA$_2$-III is released from mast cell granules, and mast cell-associated anaphylactic responses are markedly attenuated in *Pla2g3*$^{-/-}$ mice and conversely augmented in *Pla2g3*-transgenic mice (134). Tissue mast cells in *Pla2g3*$^{-/-}$ mice are immature, and therefore resistant to IgE-dependent and even IgE-independent activation. Similar mast cell abnormalities are also seen in mice lacking lipocalin-type prostaglandin D$_2$ (PGD$_2$) synthase (L-PGDS) or those lacking the PGD$_2$ receptor DP1, suggesting their functional relationship. Indeed, genetic or pharmacological inhibition of DP1 in mast cells or L-PGDS in fibroblasts phenocopies that of sPLA$_2$-III in mast cells in terms of defective mast cell maturation and anaphylaxis. Mechanistically, sPLA$_2$-III secreted from immature mast cells is coupled with fibroblastic L-PGDS to provide PGD$_2$, which in turn promotes mast cell maturation via DP1. It has long been believed that mast cell maturation requires some unknown factor(s) derived from microenvironmental fibroblasts. The PGD$_2$ driven by the sPLA$_2$-III/L-PGDS/DP1 loop provides a missing microenvironmental cue that underlies the proper maturation of mast cells (134). This paracrine loop also appears to be operative for maturation of human mast cells.

sPLA$_2$-III is highly expressed in the epididymal epithelium, where it acts on immature sperm cells passing through the duct in a paracrine manner to regulate phospholipid remodeling (135). During epididymal transit of spermatozoa, PC in the sperm membrane undergoes a dramatic shift in its acyl groups from oleic acid and AA to docosapentaenoic acid (DPA) and DHA, and the increased proportion of DPA/DHA consequently contributes to increased sperm membrane fluidity and thereby flagellar motility. This sperm membrane remodeling is severely compromised in *Pla2g3*$^{-/-}$ mice, whose spermatozoa, with a low proportion of DPA/DHA, have aberrant acrosomes and flagella with an abnormal axoneme configuration and display reduced motility and fertility (135). Thus, the two "reproductive sPLA$_2$s" (sPLA$_2$-III and -X), which are expressed in different locations within male genital organs, exert nonredundant but interrelated functions in two major steps of male fertility; the former during sperm maturation in the epididymis and the latter during capacitation and acrosome reaction, likely after ejaculation in the female genital duct.

In humans, sPLA$_2$-III is a candidate biomarker for colon cancer (136), and a *PLA2G3* haplotype is correlated with a higher risk of colon cancer (137). *PLA2G3* polymorphisms are associated with acquired immune deficiency syndrome (138). sPLA$_2$-III is induced in a human neuronal model of oxidative stress, and *PLA2G3* polymorphisms are associated with Alzheimer's disease (139). Lastly, a functional genomic screen for modulators of ciliogenesis has identified sPLA$_2$-III as a negative ciliogenesis regulator probably through regulation of the endocytic recycling pathway (140).

PLA2G12/sPLA$_2$-XII subfamily

The atypical group XII subfamily contains two isoforms, sPLA$_2$-XIIA and -XIIB. Although sPLA$_2$-XIIA is highly expressed in various tissues, its physiological functions are largely obscure because studies using *Pla2g12a*$^{-/-}$ mice have not yet been conducted. Reportedly, sPLA$_2$-XIIA kills

Gram-negative bacteria such as *Helicobacter pylori* even more efficiently than sPLA$_2$-IIA in vitro (50, 141). Ectopic overexpression of sPLA$_2$-XIIA in *Xenopus laevis* embryos leads to neurogenesis toward olfactory sensory structures (142). sPLA$_2$-XIIA is present in axon terminals and dendrites in rat brain, and injection of its antisense oligonucleotide into the prefrontal cortex results in deficits of working memory and attention (143). In humans, there is a suggestive association between a *PLA2G12A* polymorphism and response to anti-vascular endothelial growth factor therapy in patients with exudative age-related macular degeneration (144).

sPLA$_2$-XIIB, preferentially expressed in the liver, is catalytically inactive due to the replacement of the catalytic histidine by a leucine residue (16). Hepatic expression of sPLA$_2$-XIIB is induced by the transcription factor HNF-4α and its coactivator PGC-1α, and *Pla2g12b*$^{-/-}$ mice display steatohepatitis due to impaired hepatic secretion of VLDL (145). However, the molecular mechanism underlying the action of this catalytically inactive sPLA$_2$ remains fully unknown.

PLA2R1/sPLA$_2$ RECEPTOR

PLA2R1, also known as Clec13c belonging to the C-type lectin family, binds to several conventional sPLA$_2$s with distinct affinities (146). PLA2R1 exists as an integral membrane protein with a very large extracellular region comprising 10 distinct domains and only a short cytoplasmic domain, or as a soluble protein produced by alternative splicing or shedding from the membrane-bound receptor (147–149). PLA2R1 may act in three modes: *i*) as a clearance receptor that inactivates sPLA$_2$s; *ii*) as a signaling receptor that transduces sPLA$_2$-dependent signals in a catalytic activity-independent fashion; or *iii*) as a pleiotropic receptor that binds to nonsPLA$_2$ ligands.

Pla2r1$^{-/-}$ mice show lower inflammation after LPS challenge through some unknown mechanism (150). In a model of allergen-induced asthma, the lungs of *Pla2r1*$^{-/-}$ mice show greater infiltration of immune cells and higher levels of eicosanoids and Th2 cytokines, accompanied by greater levels of sPLA$_2$-IB and -X proteins, than those of wild-type mice (151), providing the first in vivo evidence that PLA2R1 serves as a clearance receptor for these sPLA$_2$s. In a model of myocardial infarction, *Pla2r1*$^{-/-}$ mice exhibit higher rates of cardiac rupture, with impaired collagen-dependent migration, growth, and activation of myofibroblasts (152). Mechanistically, binding of sPLA$_2$-IB to PLA2R1 augments the migration and growth of myofibroblasts, and thereby wound healing, through functional interaction with integrin, supporting the signaling role of PLA2R1. However, as the cardiac expression of sPLA$_2$-IB is very low, other sPLA$_2$(s) or unknown component(s) might act as a PLA2R1 ligand in this situation. Alternatively, considering that ablation of sPLA$_2$-V or -X ameliorates myocardial infarction (101, 118), the lower clearance of these sPLA$_2$s might explain the observed phenotypes in *Pla2r1*$^{-/-}$ mice. PLA2R1 may also function as a tumor suppressor by inducing cellular senescence (153–155). In line with this, *Pla2r1*$^{-/-}$ mice have increased susceptibility to skin tumorienesis due to escape from senescence (155). Although the anti-tumor function of PLA2R1 may be sPLA$_2$-independent, it is also possible that the protective effect of PLA2R1 against skin cancer is due to the clearance of a skin-resident sPLA$_2$.

Recently, PLA2R1 has been identified as a major autoantigen in membranous nephropathy, a severe autoimmune disease leading to podocyte injury and high levels of proteinuria (156, 157), suggesting that PLA2R1 is a key protein expressed in human renal podocytes. However, it is not clear whether the role of PLA2R1 in podocytes is sPLA$_2$-dependent or -independent, or whether sPLA$_2$s may play some roles in the microenvironment of the glomerulus by being supplied from the circulation or from neighboring cells such as mesangial cells, which are known to secrete sPLA$_2$-IIA under inflammatory conditions (158).

Several features of PLA2R1 pose questions regarding the signaling role of this protein. Although various sPLA$_2$s bind to mouse PLA2R1 with high to moderate affinity, this ligand specificity is not conserved in other species, including humans (146). Furthermore, unlike most signaling receptors that have a long cytoplasmic region with one or more signaling motifs, PLA2R1 possesses only a short stretch in the cytoplasmic tail without any known signaling module except for an endocytosis motif (159). With this structural property, it is difficult to envisage that PLA2R1 itself would act as a signaling receptor. Hence, the presence of a second, as yet unknown, signaling subunit that could form a functional complex with PLA2R1 should be taken into consideration. It is interesting to note that several C-type lectins can act cooperatively with other signaling receptors (160, 161). For instance, mannose-binding lectin enhances TLR2/TLR6 signaling (162), dectin-1, which recognizes a fungal component, can collaborate with TLR2 (163), and dectin-2, which does not possess an intracellular signaling motif, can transmit signals by interacting with ITAM motif-bearing receptors such as FcRγ and DAP12 (164). By analogy, PLA2R1, as a member of the C-type lectins, might be functionally coupled with other signaling receptors leading to cellular responses.

CONCLUDING REMARKS

Studies during the last decade have revealed the pathophysiological functions of various sPLA$_2$s, as exemplified by sPLA$_2$-IB, IIA, IID, IIE, V, X, and III acting as "digestive," "inflammatory or bactericidal," "resolving," "metabolic," "reproductive or anaphylactic," "Th2-prone or metabolic," and "asthmatic, reproductive, or gastrointestinal" sPLA$_2$s, respectively (Figs. 1 and 2) (64, 70, 74, 112, 121, 132, 134, 135). It is now obvious that individual sPLA$_2$s play unique and tissue-specific roles by acting on extracellular phospholipids, which include adjacent cell membranes, noncellular lipid components, and foreign phospholipids, such as those in microbes and food. The diversity of target phospholipids and products may explain why the sPLA$_2$ family

contains multiple isoforms. However, as most of our knowledge on $sPLA_2$ functions has been obtained from mouse studies, it is important to translate these studies to humans with caution. Indeed, not all of these studies might be translated into humans (as exemplified by $sPLA_2$-IIA in humans versus $sPLA_2$-IIE in mice (74)), and evidence also exists that knockout mice for the same enzyme on different backgrounds behave differently (165). Nonetheless, several functions of $sPLA_2$s in mice, as depicted in Fig. 2, appear to be conserved in humans (55, 70, 74, 93, 117, 134). Further advances in this research field and their integration for therapeutic applications are expected to benefit from improved lipidomics that will allow monitoring of individual $sPLA_2$s and associated lipid metabolisms within specific tissue niches. Hopefully, the next decade will yield a comprehensive map of the $sPLA_2$-driven lipid networks, thus allowing the therapeutic application of inhibitors for some $sPLA_2$s central to human diseases.

In the interest of brevity, the authors have referenced other reviews whenever possible and apologize to the authors of the numerous original papers that were not explicitly cited.

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