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Review

Group IID, IIE, IIF and III secreted phospholipase A_2s☆

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ABSTRACT

Among the 11 members of the secreted phospholipase A_2 (sPLA$_2$) family, group IID, IIE, IIF and III sPLA$_2$s (sPLA$_2$-IID, -IIE, -IIF and -III, respectively) are "new" isoforms in the history of sPLA$_2$ research. Relative to the better characterized sPLA$_2$s (sPLA$_2$-IB, -IIA, -V and -X), the enzymatic properties, distributions, and functions of these "new" sPLA$_2$s have remained obscure until recently. Our current studies using knockout and transgenic mice for a nearly full set of sPLA$_2$s, in combination with comprehensive lipidomics, have revealed unique and distinct roles of these "new" sPLA$_2$s in specific biological events. Thus, sPLA$_2$-IID is involved in immune suppression, sPLA$_2$-IIE in metabolic regulation and hair follicle homeostasis, sPLA$_2$-IIF in epidermal hyperplasia, and sPLA$_2$-III in male reproduction, anaphylaxis, colonic diseases, and possibly atherosclerosis. In this article, we overview current understanding of the properties and functions of these sPLA$_2$s and their underlying lipid pathways *in vivo*.

1. Introduction

As already described in other reviews in this special issue, the secreted PLA$_2$ (sPLA$_2$) family contains 10 catalytically active isoforms (IB, IIA, IIC, IID, IIE, IIF, III, V, X and XIIA) and one inactive isoform (XIIB) in mammals [1–6]. Individual sPLA$_2$s exhibit unique tissue and cellular distributions and substrate selectivity, suggesting their distinct biological roles. Historically, sPLA$_2$-IB and -IIA were purified and cloned in the 1980s, and sPLA$_2$-IIC and -V were identified by genomic sequencing of the locus close to the sPLA$_2$-IIA (*PLA2G2A*) gene in 1994 [7–11]. Soon afterwards, in the period of "sPLA$_2$ hunting" research from 1997 to the early 2000s, sPLA$_2$-IID, -IIE, -IIF, -III and -X as well as two sPLA$_2$-XII isoforms were identified by EST database searches ("new" sPLA$_2$s) by Lambeau's (a guest editor of this special issue) group, as well as by others [12–21]. There is another sPLA$_2$-related protein called otoconin-95, an inner ear structural protein that contains two catalytically inactive sPLA$_2$-like domains [22].

Among the "new" sPLA$_2$s, sPLA$_2$-IID, -IIE and -IIF are classified as conventional sPLA$_2$s (group I/II/V/X), which 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. More specifically, they are members of the group II subfamily of sPLA$_2$s, to which sPLA$_2$-IIA and –IIC, as well as sPLA$_2$-V, belong. The genes for these 6 group II subfamily sPLA$_2$s are clustered at the same chromosomal locus (chromosomes 1 and 4 in human and mouse, respectively), suggesting that they originated from a common ancestral gene [18]. In contrast, sPLA$_2$-III is an atypical sPLA$_2$ showing closer similarity to bee venom group III sPLA$_2$ than to the other mammalian sPLA$_2$s [19]. Evolutionally, the group II subfamily sPLA$_2$s exist only in vertebrates, while sPLA$_2$s in the group III branch are present in vertebrates and insects but not in nematodes. Although currently known sPLA$_2$ inhibitors can inhibit conventional sPLA$_2$s to various degrees, no agent that specifically inhibits sPLA$_2$-III or sPLA$_2$-XIIA, another class of atypical sPLA$_2$, has yet become available.

Although the properties and functions of sPLA$_2$-IB, -IIA, -V and -X (see other reviews in this special issue) have been described in

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Table 1
Biological functions of $sPLA_2$-IID, -IIE, -IIF and -III as revealed by studies using knockout (KO) and transgenic (TG) mice.

Nomenclature	General names	Distributions	Lipid mobilizations	Phenotypes in KO mice	Phenotypes in TG mice	References
PLA2G2D	$sPLA_2$-IID	Lymphoid DCs, M2 macrophages	Preferential production of ω3 PUFA-derived pro-resolving lipid mediators	Exacerbation of CHS and psoriasis	Reduction of CHS and psoriasis	[25,31]
				Increased anti-tumor immunity, Protection from skin cancer	Decreased anti-tumor immunity	[31]
			Production of PGD_2	Increased anti-viral immunity, Protection from SARS-induced pneumonia	N.D.	[46]
PLA2G2E	$sPLA_2$-IIE	Adipocytes	Hydrolysis of minor lipoprotein phospholipids (*e.g.* PE and PS)	Protection from diet-induced obesity and hyperlipidemia	N.D.	[62]
			Unknown	Age-related fat accumulation and reduced lipolysis	N.D.	[66]
		Hair follicles	Release of various unsaturated fatty acids and LPE species	Modest abnormalities in hair follicles	N.D.	[55]
PLA2G2F	$sPLA_2$-IIF	Suprabasal keratinocytes	Production of lysoplasmalogen	Protection from psoriasis, CHS and skin cancer	Spontaneous development of psoriasis-like epidermal hyperplasia and alopecia, Exacerbation of skin cancer	[45]
PLA2G3	$sPLA_2$-III	Epididymal epithelial cells	Sperm membrane phospholipid remodeling	Male hypofertility	N.D.	[93]
		Mast cells	Production of microenvironmental PGD_2	Impaired mast cell maturation and anaphylaxis	Increased mast cell maturation and anaphylaxis	[34]
		Colonic epithelial cells	Production of LPA and LPI	Protection from colonic cancer and colitis	N.D.	[92]
		Aorta[a]	Generation of LPC-rich small-dense LDL	N.D.	Exacerbation of atherosclerosis	[116]
		Skin[a]	Production of PGE_2	N.D.	Spontaneous skin inflammation	[124]

N.D.; not done.
[a] Results from TG overexpression.

numerous studies, those of other sPLA$_2$s have remained poorly understood for more than a decade. Recently, a series of studies using knockout and transgenic mice for nearly a full set of sPLA$_2$s, together with comprehensive lipidomics approaches to identify their cognate substrates (phospholipids) and products (fatty acids, lysophospholipids or their metabolites), have clarified their distinct biological roles *in vivo*. Although genes for the group II subfamily sPLA$_2$s are clustered in the same chromosome locus [18], the phenotypes observed in knockout mice for individual sPLA$_2$s are distinct (see below), implying that they do not have compensatory functions. In this review, we provide an overview of current knowledge on the properties and functions of sPLA$_2$-IID, -IIE, -IIF and -III. The roles of these sPLA$_2$s and their underlying lipid-metabolic pathways are summarized in Table 1.

2. sPLA$_2$-IID

2.1. General aspects

sPLA$_2$-IID, which is more similar to sPLA$_2$-IIA (48% homology) than to other sPLA$_2$s, was identified by three groups; Lambeau's group [14] and Hanasaki's group [13] independently identified the mouse and human enzymes by EST database searches, and another group isolated sPLA$_2$-IID (called SPLASH) by subtraction cloning of splenic cDNA from wild-type (WT) and lymphotoxin-deficient mice, which have profound defects in the splenic microarchitecture [15]. Similar to sPLA$_2$-IIA, sPLA$_2$-IID is a basic protein (pI ~ 8.7) made up of 125 amino acids with 14 cysteines at exactly conserved positions. Likely because of its cationic nature, sPLA$_2$-IID binds to heparin *in vitro* or heparan sulfate on the cell surface when overexpressed in cultured cells [23].

Initial studies revealed that recombinant sPLA$_2$-IID had rather lower enzymatic activity than sPLA$_2$-IIA in an assay using phospholipid vesicles with oleic acid (OA) or linoleic acid (LA) at the *sn*-2 position [14] and that transfection of sPLA$_2$-IID into cultured cells (*e.g.* HEK293 cells) was able to augment IL-1β-induced arachidonic acid (AA) release and prostaglandin E_2 (PGE_2) generation, albeit at a lower potency than sPLA$_2$-IIA [23,24]. However, these properties need to be interpreted with caution, since PLA$_2$ enzyme assays employing artificial phospholipid vesicles comprising only one or a few phospholipid species, or cell-based studies in which sPLA$_2$s are artificially overexpressed, or in which excess sPLA$_2$s are added at super-physiological levels, do not necessarily reflect their true functional aspects *in vivo*. To comprehensively understand the pathophysiological functions of sPLA$_2$s, it is important to consider as to when, where and to what degree any given sPLA$_2$ is expressed, which phospholipid species in a given membrane component serve as the target substrates, which lipid metabolites are generated, and how these lipid metabolites modulate biological responses in relevant tissue microenvironments. It has become obvious that the functions of sPLA$_2$s are not limited to the regulation of AA metabolism, which used to be the classical view in PLA$_2$ research, but are also associated with mobilization of various fatty acids and lysophospholipids in specific tissue contexts, as described below.

sPLA$_2$-IID is expressed mainly in dendritic cells (DCs) and macrophages, particularly $CD4^+CD11b^+CD11c^+$MHC class II^{lo} DCs and M2-like macrophages, in secondary lymphoid organs such as the spleen and lymph nodes (LNs) of mice and humans [25]. As opposed to sPLA$_2$-IIA (a so-called "inflammatory sPLA$_2$"), whose expression is upregulated in various tissues in response to pro-inflammatory cytokines and lipopolysaccharide (LPS) [26], sPLA$_2$-IID is downregulated in antigen-activated MHC class II^{hi} DCs [25] or LPS-stimulated tissues and macrophages [16,27]. A new lipidomics-based PLA$_2$ enzyme assay using a natural phospholipid mixture extracted from a relevant tissue (lymphoid tissues in the case of sPLA$_2$-IID) as a substrate ("natural membrane assay" [28]) has revealed that sPLA$_2$-IID preferentially hydrolyzes phosphatidylethanolamine (PE) species with *sn*-2 polyunsaturated fatty acids (PUFAs), including ω6 AA and more efficiently ω3 eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), rather than those with OA and LA [25]. This enzymatic preference of sPLA$_2$-IID for PE species with ω3 PUFAs as substrates, together with its distribution in lymphoid immune cells and downregulation by pro-inflammatory stimuli, suggests that sPLA$_2$-IID has a role in resolution, rather than promotion, of the adaptive immune response.

2.2. Suppression of adaptive immune responses

The possibility that sPLA$_2$-IID might have an immunosuppressive function was first demonstrated in the research field of T cell biology. Von Allmen et al. found that, among the various T cell subsets, sPLA$_2$-IID is selectively expressed in T_{reg} cells and has the capacity to promote T_{reg} differentiation and function [29], although a subsequent study has shown that sPLA$_2$-IID is expressed much more abundantly in antigen-presenting cells (DCs and macrophages) than in T_{reg} cells [25]. Interestingly, an sPLA$_2$-IID-Fc fusion protein inhibits the proliferation of $CD4^+$ and $CD8^+$ effector T cells *in vitro* and suppresses Th17-dependent diseases such as colitis and multiple sclerosis when administered to mice. However, it remained uncertain whether systemically administered artificial sPLA$_2$-IID-Fc fusion protein indeed mirrored the intrinsic function of endogenous sPLA$_2$-IID, and even if so, how this enzyme exerts its immunoregulatory functions. Although the sPLA$_2$-IID-Fc fusion protein might act on the sPLA$_2$ receptor (PLA2R1), sPLA$_2$-IID has poor binding affinity for PLA2R1 [30] (overall binding properties of various sPLA$_2$s to PLA2R1 are detailed in the other review in this special issue). Beyond this, the possibility that sPLA$_2$-IID could transmit some signals through binding to an unknown receptor cannot be ruled out, and the distinction between an effect due to enzymatic activity *versus* a receptor-operated mechanism can only be addressed by using a catalytic mutant of sPLA$_2$-IID, including knock-in mice such as the sPLA$_2$-IID mutant "H48Q". Nonetheless, the immunosuppressive function of sPLA$_2$-IID has been established by a series of recent studies using sPLA$_2$-IID-deficient (*Pla2g2d*$^{-/-}$) and -transgenic (*Pla2g2d*-TG) mice, as described below.

In a model of Th1-dependent contact hypersensitivity (CHS), application of the hapten antigen dinitrofluorobenzene (DNFB) to abdominal skin (sensitization) followed by a second application of the same antigen to ear skin (elicitation) induces ear swelling. In the elicitation phase of CHS, the resolution, but not propagation, of inflammation in the skin and LNs is delayed in *Pla2g2d*$^{-/-}$ mice [25]. In this state, expression levels of the signature Th1 cytokines IFN-γ and IL-12 are highly elevated in the draining LNs, whereas those of the T_{reg} markers FOXP3 and IL-10 are unaffected, by sPLA$_2$-IID deficiency. Even in the late stage of the sensitization phase, IFN-γ expression in the LNs is substantially elevated in *Pla2g2d*$^{-/-}$ mice [31]. Moreover, DCs isolated from *Pla2g2d*$^{-/-}$ mice are hyper-activated even in the absence of stimulation, with increased secretion of IFN-γ and elevated surface expression of MHC class II [25]. In contrast, acute skin inflammation as evaluated by irritant dermatitis is not affected by sPLA$_2$-IID deficiency [31]. These results suggest that the lack of sPLA$_2$-IID augments DC-mediated Th1 immunity, rather than influencing T_{reg} cell function and neutrophil-mediated acute inflammation.

Psoriasis is a common chronic skin diseases in western countries, characterized by epidermal hyperplasia (acanthosis), scaling, and erythematous plaque formation due to aberrant proliferation, differentiation and activation of keratinocytes as well as activation of Th17-type immunity [32]. In a model of imiquimod (IMQ)-induced psoriasis, *Pla2g2d*$^{-/-}$ mice display more severe epidermal hyperplasia than do *Pla2g2d*$^{+/+}$ mice, with increased IL-17A$^+$ or IL-22$^+$ T cells in the affected skin and regional LNs [31]. Furthermore, DCs from *Pla2g2d*$^{-/-}$ mice produce greater amounts of IL-6 and IL-23, which play pivotal roles in Th17 immunity [33], than those from WT mice. Conversely, *Pla2g2d*-TG mice display milder inflammation in the CHS and psoriasis models [31]. Thus, sPLA$_2$-IID suppresses the Th1- and Th17-dependent adaptive immune responses in CHS and psoriasis, respectively. This concept appears to corroborate the ability of a sPLA$_2$-IID-Fc fusion

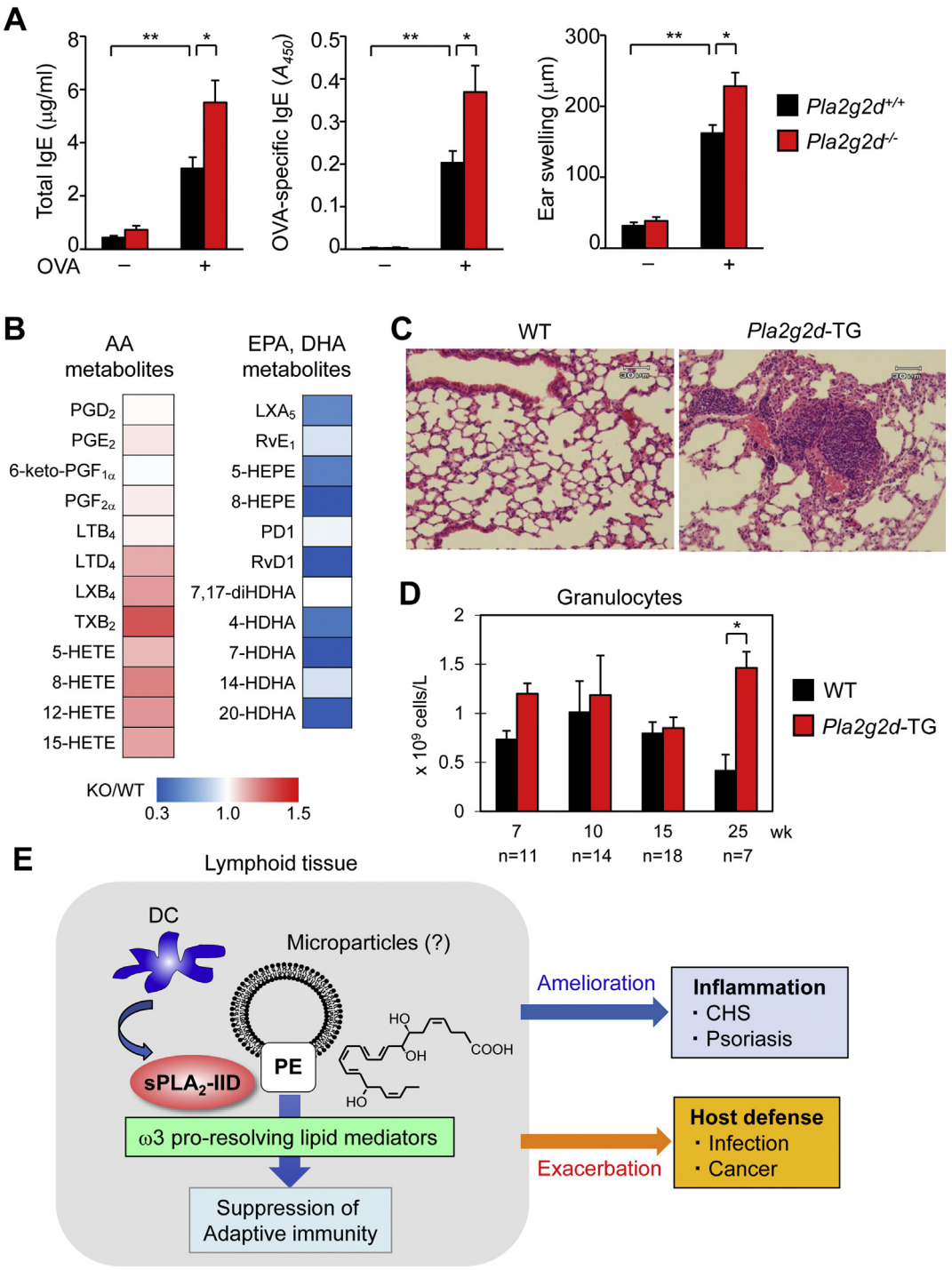

Fig. 1. Properties and functions of sPLA$_2$-IID. (A) Increased Th2 response in *Pla2g2d*$^{-/-}$ mice. *Pla2g2d*$^{+/+}$ and *Pla2g2d*$^{-/-}$ mice (male, 8 weeks old) were immunized intraperitoneally on days 0, 7, and 14 with 10 μg of chicken OVA (Sigma-Aldrich) in 100 μl of saline mixed with 200 μl of alum (Alu Gel S, which contained 2% Al(OH)$_3$; Serva). Seven days after the last immunization, the left and right ears of the mice were injected intradermally with 30 μg of OVA. Ear swelling was measured at 30 min after OVA challenge. Total and OVA-specific IgE levels in sera were measured by ELISA (Bethyl Laboratories). OVA-induced IgE levels and ear edema were elevated in *Pla2g2d*$^{-/-}$ mice relative to *Pla2g2d*$^{+/+}$ mice (n = 5–7, mean ± SEM, *$p < 0.05$, **$p < 0.01$). (B) Lipidomic heat map profiling of ω6 AA- and ω3 EPA/DHA-derived lipid mediators in lymph nodes of *Pla2g2d*$^{-/-}$ (KO) mice relative to *Pla2g2d*$^{+/+}$ (WT) mice. EPA/DHA-derived lipid mediators were decreased in KO mice [25,31]. The elevation of several AA metabolites in KO mice might have been due to increased lymph node inflammation. HETE, hydroxyeicosatetraenoic acid; HEPE, hydroxyeicosapentaenoic acid; HDHA, hydroxydocosahexaenoic acid; LX, lipoxin; PD, protectin; Rv, resolvin. (C) Lung histology of WT and *Pla2g2d*-TG mice (male, 34 weeks old). The lungs of *Pla2g2d*-TG mice had more pronounced leukocyte infiltration than those of WT mice. (D) Aged (25 weeks old), but not young (7–15 weeks old), *Pla2g2d*-TG mice had more circulating granulocytes than did age-matched WT mice (mean ± SEM, *$p < 0.05$). The results in (C, D) suggest that the increased immunosuppressive tone in the TG mice results in more opportunistic infection, and thereby airway inflammation. (E) A schematic diagram of sPLA$_2$-IID action. In lymphoid tissues, sPLA$_2$-IID is preferentially expressed in DCs and hydrolyzes PE in microparticles to provide ω3 EPA/DHA-derived pro-resolving lipid mediators (the structure of RvD1 is shown), which dampen adaptive immunity. As such, sPLA$_2$-IID ameliorates Th1/Th17-dependent inflammation in CHS and psoriasis and perturbs host defense against infection and cancer.

protein to suppress colitis and multiple sclerosis, which are typical Th17-dependent disease models [29].

To address whether or not sPLA$_2$-IID would also affect Th2 immunity, we sensitized *Pla2g2d*$^{-/-}$ and littermate *Pla2g2d*$^{+/+}$ mice with ovalbumin (OVA) intraperitoneally and challenged them with the same antigen into the ears. In this model of Th2-dependent active cutaneous anaphylaxis, the serum levels of total and OVA-specific IgE, as well as ear swelling, were significantly increased in OVA-challenged *Pla2g2d*$^{-/-}$ mice relative to *Pla2g2d*$^{+/+}$ mice (Fig. 1A). Since passive cutaneous anaphylaxis is not affected by the absence of sPLA$_2$-IID [34], it is likely that the increased active anaphylactic response in *Pla2g2d*$^{-/-}$ mice is due to an increased level of OVA-specific IgE (an indication of the increased Th2 response) and thereby hyper-activation of mast cells sensitized by this IgE, rather than being attributable to some intrinsic alterations in mast cells or vascular endothelial cells. Thus, not only Th1/Th17 immunity, but also the Th2-dependent immune response is suppressed by sPLA$_2$-IID.

Lipidomics analyses of regional LNs and spleen, where sPLA$_2$-IID is abundantly expressed, have revealed that the steady-state levels of ω3 PUFAs are markedly reduced in *Pla2g2d*$^{-/-}$ mice relative to *Pla2g2d*$^{+/+}$ mice [25,31]. Moreover, the levels of ω3 PUFA metabolites, such as DHA-derived resolvin D1 (RvD1), are markedly lower in *Pla2g2d*$^{-/-}$ LNs than in *Pla2g2d*$^{+/+}$ LNs (Fig. 1B). Conversely, the levels of ω3 PUFA metabolites are elevated in the LNs of *Pla2g2d*-TG mice relative to WT mice [31]. In contrast, the LN levels of eicosanoids (prostanoids and leukotrienes) are barely altered or even elevated by sPLA$_2$-IID deletion, implying that these AA metabolites are largely derived from a sPLA$_2$-IID-independent AA pool, possibly through the action of cytosolic PLA$_2$ (cPLA$_2$α) or other PLA$_2$ subtype(s). Together with the substrate selectivity described above, it is likely that sPLA$_2$-IID preferentially and constitutively hydrolyzes PUFA-containing PE species in LN membranes, probably those in microparticles (as in the case of sPLA$_2$-IIA) [35,36], to mobilize ω3 PUFA-derived anti-inflammatory lipid mediators, which can put a brake on DC-committed adaptive immunity. It has been reported that leukocyte-derived microparticles spatiotemporally generated in inflammatory exudates during resolution contain esterified phospholipid precursors of anti-inflammatory lipid mediators [37]. We therefore speculate that similar microparticles constitutively generated in lymphoid tissues might be a target of sPLA$_2$-IID, although this hypothesis needs further elucidation. A growing body of evidence indicates that ω3 PUFA-derived resolvins including RvD1 have the capacity to suppress acquired immunity by attenuating migration and activation of DCs, antigen presentation to T cells, and IgE class switching in B cells [31,38–41]. Furthermore, consistent with the view that some ω3 PUFA metabolites such as maresins facilitate anti-inflammatory M2 polarization of macrophages [42,43], the splenic ratio of M2/M1 macrophages is decreased in *Pla2g2d*$^{-/-}$ mice relative to WT mice [31].

Collectively, sPLA$_2$-IID is a "resolving sPLA$_2$" that preferentially mobilizes ω3 PUFA metabolites in lymphoid organs, thereby ameliorating aggravated adaptive immunity. It should be noted that sPLA$_2$-IID is not the only ω3 PUFA-releasing sPLA$_2$ *in vivo*. Indeed, ω3 PUFAs are released by sPLA$_2$-X in the colon and spermatozoa [44] and by sPLA$_2$-IIF in the skin [45], where each of these sPLA$_2$s has tissue-specific roles (see below).

2.3. Suppression of anti-viral and anti-tumor immunity

Although sPLA$_2$-IID prevents exaggerated Th1/Th17 immunity in CHS and psoriasis, this beneficial immunosuppressive property is conversely disadvantageous in some circumstances such as host defense against infection and cancer. Indeed, sPLA$_2$-IID prevents anti-viral and anti-tumor Th1 immunity, eventually exacerbating viral infection and tumor development toward worse outcomes.

sPLA$_2$-IID expression in lung DCs increases with age in response to chronic exposure to oxidative stress. In aged (10–13 months old) mice, sPLA$_2$-IID contributes to exacerbation, rather than amelioration, of pneumonia caused by infection with SARS coronavirus or influenza virus [46]. In this situation, sPLA$_2$-IID is coupled with pulmonary mobilization of prostaglandin D$_2$ (PGD$_2$), an anti-inflammatory AA metabolite in this context that blocks DC migration and thereby Th1-driven anti-viral responses through its receptor, DP1. Accordingly, *Pla2g2d*$^{-/-}$ mice show increased migration of lung DCs to LNs, leading to augmented anti-viral T cell responses, which are protective against infection-induced lung inflammation and death. Although not tested in that study, it is conceivable that the steady-state reduction of ω3 PUFA metabolites in the LNs of *Pla2g2d*$^{-/-}$ mice (see above) may also contribute to the increased anti-viral immunity in this setting. Consistent with this notion, aged (> 6 months old) *Pla2g2d*-TG mice show more profound leukocyte infiltration in the lung (Fig. 1C) and more granulocytes in the circulation (Fig. 1D) than age-matched WT mice, suggesting that the increased immunosuppressive tone by overexpression of sPLA$_2$-IID results in more opportunistic infection and thereby lung inflammation.

Likewise, sPLA$_2$-IID accelerates, rather than prevents, the development of skin tumors, likely because this enzyme attenuates anti-tumor Th1 immunity. In a model of chemical carcinogenesis, *Pla2g2d*$^{-/-}$ mice are highly protected against the development of skin cancer, accompanied by an increase of cytotoxic CD8α$^+$IFN-γ$^+$ T cells and M1-like macrophages, as well as a decrease of tumor-promoting M2-like macrophages [31]. Conversely, transgenic overexpression of sPLA$_2$-IID shifts the immune balance toward suppression of the anti-tumor immunity. Reportedly, ectopic administration of ω3 PUFA metabolites [31,47,48] or systemic overproduction of these lipids in mice transgenic for *Fat-1* (an ω3 PUFA synthase in *Caenorhabditis elegans*) [49] confers protective effects against infection-based inflammation or cancer xenograft by facilitating phagocytotic clearance of detrimental materials by neutrophils and macrophages. Apart from this systemic effect of ω3 PUFAs, the spatiotemporal supply of ω3 PUFAs by sPLA$_2$-IID in local lymphoid niches may have a distinct impact on adaptive immunity by suppressing the functions of DCs and T cells.

Taken together, the immunosuppressive functions of sPLA$_2$-IID provide favorable or unfavorable outcomes in distinct disease settings, protecting against inflammation and exacerbating infection and cancer (Fig. 1E). This points to the potential prophylactic or therapeutic use of an agent that would specifically stabilize or inhibit this enzyme according to disease context. In particular, specific inhibition of sPLA$_2$-IID in patients with severe respiratory infection or those with certain types of cancer would be a potentially attractive therapeutic intervention for restoration of immunological functions, a concept reminiscent of the "immune checkpoint" therapy.

2.4. Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality worldwide. This life-threatening disease not only creates problems resulting from airflow obstruction, but also has a major impact on cardiac function and air exchange, thereby resulting in systemic manifestations [50,51]. The presence of chronic and systemic inflammatory responses has an important influence on patient survival, because unexplained weight loss due to muscle wasting and adipose tissue depletion, a characteristic feature of advanced COPD, can be linked to systemic inflammation.

Interestingly, G80S polymorphism in the human sPLA$_2$-IID (*PLA2G2D*) gene is associated with body weight loss in patients with COPD [52]. COPD patients carrying sPLA$_2$-IID(Ser80) lose a significant amount of body weight in comparison with those carrying sPLA$_2$-IID (Gly80). Although this mutation does not affect the *in vitro* enzymatic activity of sPLA$_2$-IID, it enhances the expression of IL-6 and IL-8 in A549 cells (a human pulmonary epithelial cell line) [53]. A molecular model of human sPLA$_2$-IID has revealed substantial differences between the native and mutant forms in terms of channel opening and the

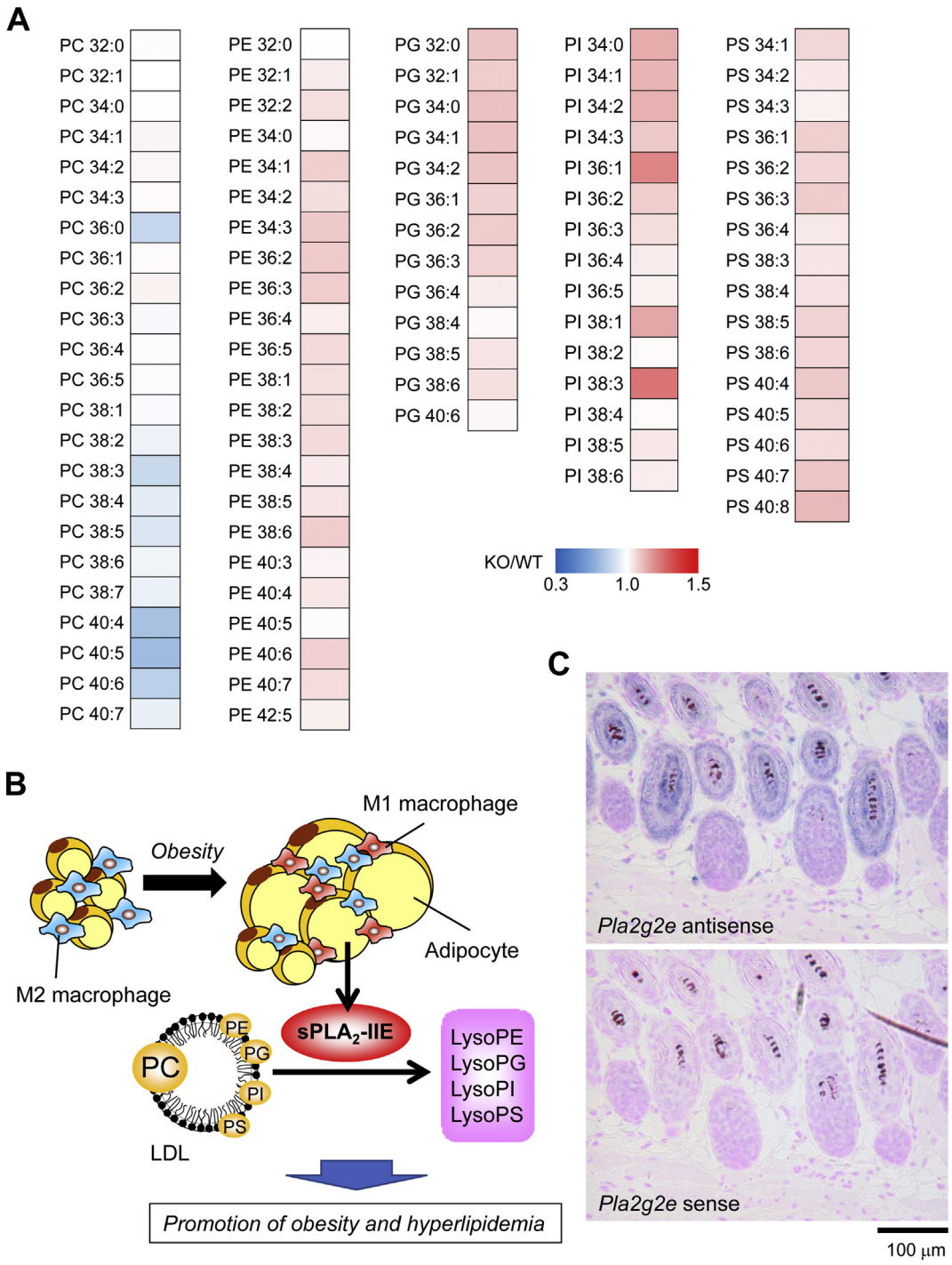

Fig. 2. Properties and functions of sPLA$_2$-IIE. (A) Lipidomic heat map profiling of phospholipids in LDL of *Pla2g2e*$^{-/-}$ (KO) mice relative to *Pla2g2e*$^{+/+}$ (WT) mice fed a high-fat diet for 18 weeks. Most PE, PG, PI and PS molecular species were elevated in LDL of KO mice, suggesting that sPLA$_2$-IIE acts on these minor lipoprotein phospholipids with no apparent fatty acid selectivity [62]. (B) A schematic diagram of the sPLA$_2$-IIE-driven lipid pathway in lipoprotein metabolism during obesity. In obesity, sPLA$_2$-IIE is induced in adipocytes, hydrolyzes minor lipoprotein phospholipids, and promotes obesity and hyperlipidemia. The roles of lysophospholipids released by sPLA$_2$-IIE are unknown. (C) *In situ* hybridization of sPLA$_2$-IIE in mouse skin. Intense *Pla2g2e* signal are localized to hair follicles [55].

surface area for interfacial binding contact [54]. Given the immunosuppressive property of sPLA$_2$-IID described above, the Ser80 mutant form might have weaker ability than the Gly80 native form to suppress inflammation. It is also possible that the body weight loss could be related to the anti-inflammatory function of sPLA$_2$-IID in metabolically active tissues (*e.g.* adipose tissue), which will be described elsewhere.

3. sPLA$_2$-IIE

3.1. General aspects

Mouse and human sPLA$_2$-IIEs were identified by Lambeau's group [17] and Hanasaki's group [16] from the EST databases. sPLA$_2$-IIE consists of 123 amino acids and is most similar to sPLA$_2$-IIA with respect to the number and positions of cysteine residues as well as overall

identity (51% homology). Similar to other group II subfamily $sPLA_2$s (except for $sPLA_2$-IIF; see below), $sPLA_2$-IIE is a basic protein (pI ~ 8.1) and shows weak affinity for heparin. Within the limitations of the overexpression strategy using cultured cells, the ability of $sPLA_2$-IIE to elicit AA release is weaker than that of $sPLA_2$-IID [23,24].

Valentin et al. have reported that the enzymatic activity of $sPLA_2$-IIE is much weaker than that of other $sPLA_2$s [17], whereas Suzuki et al. have shown that the activity of $sPLA_2$-IIE is comparable to that of $sPLA_2$-IIA, hydrolyzing PE and to a lesser extent phosphatidylcholine (PC) with no fatty acid selectivity [16]. To reconcile the inconsistency between those two studies, we reevaluated the enzymatic activity of $sPLA_2$-IIE using a lipidomics-based natural membrane assay with a phospholipid mixture extracted from mouse skin, a tissue where $sPLA_2$-IIE is expressed abundantly (see below), as a substrate. It was found that $sPLA_2$-IIE is as active as other $sPLA_2$s if the phospholipid concentration is sufficiently high, whereas its activity is very weak at a low substrate concentration that allows other $sPLA_2$s to remain fully active [55]. This suggests that the apparent K_m of $sPLA_2$-IIE toward this skin-extracted phospholipid mixture is higher than that of other $sPLA_2$s. In the presence of a sufficiently high concentration of phospholipids, $sPLA_2$-IIE is capable of releasing various unsaturated fatty acids including OA, LA, AA and DHA as well as lysphosphatidylethanolamine (LPE) in preference to lysophosphatidylcholine (LPC), a pattern similar to the results reported by Suzuki et al. [16]. This substrate selectivity is further supported by the crystal structure of human $sPLA_2$-IIE, which shows overall similarity to that of human $sPLA_2$-IIA, yet with substantial differences in terms of basic residue clusters at the interfacial site and C-terminal region [56].

In some inbred mouse strains such as C57BL/6, A/J, C58/J, P/J, 129/Sv and B10.RIII, $sPLA_2$-IIA is entirely absent due to a frameshift mutation in its gene, whereas the gene is functional, but its expression is largely restricted to the intestine, in inbred strains such as BALB/c, C3H, NZB and DBA and outbred strains such as OF1 [57]. Instead, $sPLA_2$-IIE expression is markedly induced in several mouse tissues upon LPS challenge [16]. Serum amyloid A, a pro-inflammatory mediator of lethal systemic inflammatory diseases, induces $sPLA_2$-IIE expression in mouse macrophages [58]. In contrast, $sPLA_2$-IIE expression is barely detectable in most human tissues, leading to the hypothesis that the functions of $sPLA_2$-IIA in humans might be compensated by $sPLA_2$-IIE in mice [4]. Nevertheless, a few studies have reported that $sPLA_2$-IIE is expressed in human cells [59,60] and that polymorphism in the human $sPLA_2$-IIE (*PLA2G2E*) gene is associated with ulcerative colitis [61], suggesting that $sPLA_2$-IIE may be functional in humans in certain situations. Recent studies using $sPLA_2$-IIE-deficient (*Pla2g2e*$^{-/-}$) mice have revealed the novel roles of this $sPLA_2$ in metabolic regulation and hair follicle homeostasis, as described below.

3.2. Metabolic regulation

$sPLA_2$-IIE is highly induced in hypertrophic white adipocytes in mice fed a high-fat diet or in genetically obese *ob/ob* mice [62]. An adipogenic stimulus is sufficient for the induction of $sPLA_2$-IIE in 3T3-L1 adipocytes. In a model of diet-induced obesity, *Pla2g2e*$^{-/-}$ mice are modestly protected from obesity, hepatic steatosis and hyperlipidemia [62]. Lipidomics analysis of plasma lipoproteins obtained from *Pla2g2e*$^{-/-}$ mice in comparison with *Pla2g2e*$^{+/+}$ mice has revealed that various molecular species of PE, phosphatidylserine (PS), phosphatidylinositol (PI) and phosphatidylglycerol (PG), but not those of PC, are all elevated in the null mice (Fig. 2A), suggesting that $sPLA_2$-IIE preferentially hydrolyzes these minor lipoprotein phospholipids with no apparent fatty acid selectivity *in vivo* [62]. As such, $sPLA_2$-IIE, a "metabolic $sPLA_2$", alters the lipid composition of lipoproteins, thereby moderately affecting lipid accumulation in adipose tissue and liver (Fig. 2B). However, the mechanism whereby the $sPLA_2$-IIE-driven hydrolysis of minor lipoprotein phospholipids is linked to metabolic regulation still remains obscure. Since an increase of negative charges in lipoproteins renders the particles smaller [63], an increase of anionic phospholipids (*e.g.* PS) in lipoproteins resulting from $sPLA_2$-IIE deficiency might afford such an effect. Alternatively, certain lysophospholipid species produced by $sPLA_2$-IIE might have some metabolic effects, a possibility that awaits future studies. In fact, lysophosphatidylserine (LysoPS) and lysophsophatidylinositol (LPI) act on their cognate receptors that can affect inflammation and metabolism [64,65]. Importantly, the metabolic action of $sPLA_2$-IIE contrasts with that of $sPLA_2$-V, another diet-inducible "metabolic $sPLA_2$" that hydrolyzes PC in low-density lipoprotein (LDL) to preferentially release OA and LA, thereby protecting against obesity, insulin resistance, fatty liver, and adipose tissue inflammation [62].

On the other hand, another study has revealed that *Pla2g2e*$^{-/-}$ mice accumulate more epididymal fat than do *Pla2g2e*$^{+/+}$ mice as they age [66]. During *ex vivo* adipogenesis, knockout or knockdown of $sPLA_2$-IIE increases triglycerides in adipocytes, whereas its overexpression or exogenous addition facilitates lipolysis with increased release of glycerol. Although the reason for the discrepancy between these two studies is unclear, it might be attributable to the difference of experimental conditions (diet-induced *versus* age-associated obesity, high-fat *versus* chow diet, or female *versus* male) in the different animal facilities. One possible explanation is that $sPLA_2$-IIE might have some additional effects on brown or beige fat, and thereby lipolysis and thermogenesis, a hypothesis that remains to be tested.

3.3. Hair follicle homeostasis

Hair follicles in the skin undergo repeated cycles of growth (anagen), regression (catagen) and rest (telogen) during life [67]. Perturbed skin lipid metabolism variably and often severely affects hair cycling, thereby causing hair loss or alopecia [68,69]. $sPLA_2$-IIE is a "hair follicular $sPLA_2$" that is expressed abundantly in hair follicles during the anagen period, being distributed in companion cells of the outer root sheath and cuticular cells of the inner root sheath [55] (Fig. 2C). *Pla2g2e*$^{-/-}$ mice exhibit mild skin abnormalities with perturbation of hair follicle ultrastructure and modest changes in the steady-state expression of a subset of skin genes. Lipidomics analysis has revealed that $sPLA_2$-IIE mobilizes various unsaturated fatty acids and LPE species (both acyl and plasmalogen forms) in mouse skin. This substrate selectivity fits well with the *in vitro* enzymatic property of $sPLA_2$-IIE (see above). However, it remains unclear which lipid metabolites mobilized by $sPLA_2$-IIE are important for hair follicle homeostasis.

4. $sPLA_2$-IIF

4.1. General aspects

Mouse and human $sPLA_2$-IIFs were identified by Lambeau and his colleagues [17,18]. $sPLA_2$-IIF consists of 148 amino acids harboring all of the structural features of group II subfamily $sPLA_2$s, but has several unique characteristics. First, $sPLA_2$-IIF is an acidic protein (pI ~ 5.8), in contrast to the other group II subfamily $sPLA_2$s, which are basic. Second, although $sPLA_2$s are active under neutral to mildly basic conditions in general, $sPLA_2$-IIF retains its full enzymatic activity even at mildly acidic pH. This property may be related to the distribution of the enzyme in the epidermis (see below), where a mildly acidic environment is important for proper keratinocyte differentiation and function [70]. Third, $sPLA_2$-IIF has a uniquely long C-terminal extension that is proline-rich and contains a single cysteine. The presence of this odd cysteine raises the possibility that $sPLA_2$-IIF might occur as a covalent dimer (like several venom $sPLA_2$s), although this has not been experimentally confirmed. Fourth, $sPLA_2$-IIF is more hydrophobic than other $sPLA_2$s. Probably as a result of this high hydrophobicity, $sPLA_2$-IIF has a unique ability to penetrate and disrupt lipid monolayers and bilayers *in vitro* and to rapidly enter HEK293 cells in an endocytosis-independent

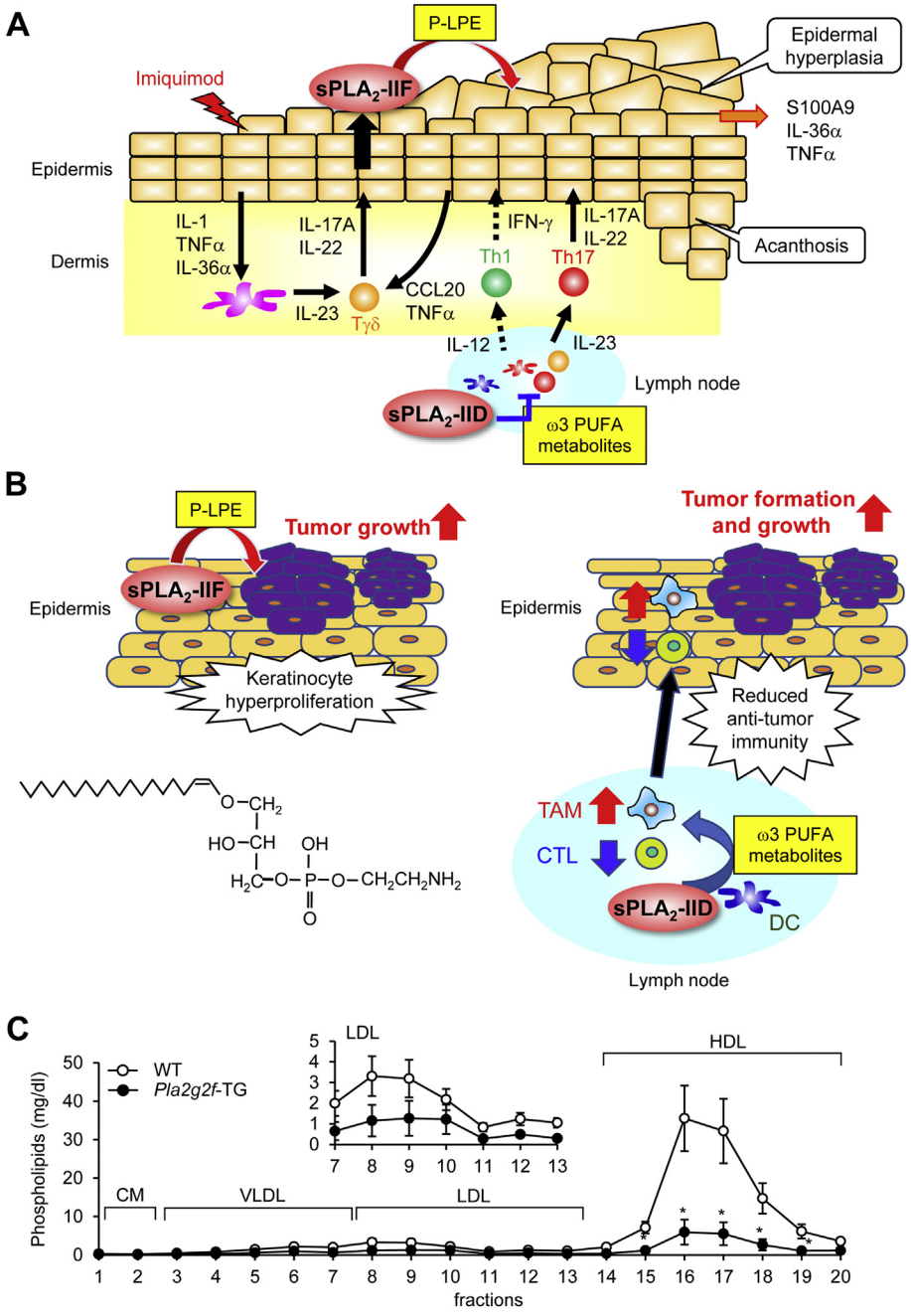

Fig. 3. Properties and functions of $sPLA_2$-IIF. (A, B) Distinct roles of $sPLA_2$-IIF and $sPLA_2$-IID in psoriasis and skin cancer [31,45]. (A) Following a psoriatic stimulus (imiquimod), $sPLA_2$-IIF is induced in epidermal keratinocytes by Th17 cytokines derived from Tγδ and Th17 cells and hydrolyzes plasmalogen to give rise to lysoplasmalogen (P-LPE), which in turn promotes epidermal hyperplasia and inflammation. In contrast, $sPLA_2$-IID blocks Th17 immunity in lymph nodes through production of ω3 PUFA metabolites, thereby putting a brake on psoriasis. (B) P-LPE produced by epidermal $sPLA_2$-IIF promotes hypergrowth of skin cancer, without affecting its incidence. In contrast, ω3 PUFA metabolites produced by $sPLA_2$-IID in lymph nodes decrease IFN-γ^+CD8$^+$ cytotoxic T cells (CTLs) and increase M2-like tumor-associated macrophages (TAMs), leading to reduced anti-tumor immunity. As such, $sPLA_2$-IID facilitates tumor formation and growth. The structure of P-LPE is shown. (C) Lipoprotein profiles in *Pla2g2f*-TG and WT mice. The levels of phospholipids in HDL and LDL were markedly lower in *Pla2g2f*-TG mice than in WT mice (n = 4, mean ± SEM, $*p < 0.05$), suggesting that $sPLA_2$-IIF, when overexpressed systematically, has the capacity to hydrolyze lipoprotein phospholipids in the circulation. LDL fractions are magnified in *Inset*. VLDL, very-low-density lipoprotein; HDL, high-density lipoprotein; CM, chylomicron.

manner to form unusual aggregates [71]. Within the limitations of the overexpression strategy, $sPLA_2$-IIF can increase AA release with a potency comparable to $sPLA_2$-III and superior to $sPLA_2$-IIA when transfected into HEK293 cells or human fibroblasts (the rank order is X > V > III = IIF > IIA > IID > IIE) [24,72]. In the natural membrane assay using a phospholipid mixture extracted from mouse skin, $sPLA_2$-IIF preferentially hydrolyzes PE, particularly plasmalogen-type PE (P-PE), to yield lysoplasmalogen (plasmalogen-type LPE; P-LPE) as well as DHA in preference to AA at a physiologically relevant concentration [45]. Of note, although high concentrations of $sPLA_2$s often cleave all substrates non-selectively *in vitro*, as we have observed in skin lipid hydrolysis by recombinant $sPLA_2$-IIF [45,55], the use of low concentrations of $sPLA_2$s could reproduce the *in vivo* substrate selectivity in the natural membrane assay.

The epidermis is a highly organized stratified epithelium having four distinctive layers comprising the innermost stratum basale, the stratum spinosum, the stratum granulosum, and the outermost stratum corneum (SC) [73]. $sPLA_2$-IIF is abundantly expressed in the suprabasal (spinous to SC) layers of the epidermis [45]. In cultured keratinocytes, $sPLA_2$-IIF is markedly increased during cell differentiation in parallel with the induction of keratinocyte differentiation and activation markers such as KRT1, S100A9 and IL-36α, and robustly upregulated following stimulation with the Th17 cytokines IL-22 and IL-17A [45]. Moreover, $sPLA_2$-IIF is highly expressed in the hyperplasic epidermis of patients with psoriasis [45]. These findings indicate that $sPLA_2$-IIF may be associated with epidermal homeostasis and diseases, particularly with the pathology of psoriasis in which Th17 immunity plays a crucial role. Indeed, studies using $sPLA_2$-IIF-deficient (*Pla2g2f*$^{-/-}$) and transgenic (*Pla2g2f*-TG) mice have revealed the unique role of $sPLA_2$-IIF, an "epidermal $sPLA_2$", in epidermal hyperplasic diseases including psoriasis and skin cancer, as described below.

4.2. Psoriasis

Perturbation of epidermal lipids variably and often profoundly affects skin homeostasis and barrier function, leading to skin disorders such as ichthyosis, psoriasis, atopic dermatitis and cancer [74–76]. Prior to the discovery of epidermal expression of sPLA$_2$-IIF, it was recognized that several sPLA$_2$s are expressed in mouse and human skins [77–80]. Interestingly, transgenic overexpression of human sPLA$_2$-IIA (*PLA2G2A*-TG) or sPLA$_2$-X (*PLA2G10*-TG) in mice led to epidermal hyperplasia and alopecia [81–83], although endogenous expression of these two sPLA$_2$s has been scarcely detected in mouse skin [45]. Later, it was shown that global or skin-specific *Pla2g2f*-TG mice spontaneously develop psoriasis-like epidermal hyperplasia and alopecia, with increased expression of a panel of psoriasis markers including S100A9 and IL-36α. Therefore, the skin phenotypes observed in *PLA2G2A*-TG or *PLA2G10*-TG mice may indicate that sPLA$_2$-IIA or -X mimic the intrinsic actions of sPLA$_2$-IIF when artificially overexpressed in the skin or that endogenous sPLA$_2$-IIF is upregulated in the hyperplasic epidermis of these TG mice.

Pla2g2f$^{-/-}$ mice exhibit only mild skin abnormalities under the basal state, characterized by a fragile stratum corneum with modest perturbation of skin barrier function and acidity [45]. These phenotypes are evident in the abdominal, but not dorsal, skin of adult, but not newborn, *Pla2g2f*$^{-/-}$ mice, suggesting that sPLA$_2$-IIF contributes to SC stability against environmental stresses, such as friction against the floor or prolonged exposure to skin microbiota, rather than to the central program of epidermal differentiation. After tape-stripping of the corneum, *Pla2g2f*$^{-/-}$ mice display delayed recovery from the skin barrier damage [80], suggesting that sPLA$_2$-IIF accelerates epidermal repair. The impact of sPLA$_2$-IIF ablation is more dramatic in primary keratinocytes, where the cells fail to be differentiated and undergo proper activation when sPLA$_2$-IIF is genetically or pharmacologically inactivated [45]. The more profound effects of sPLA$_2$-IIF deletion on keratinocytes *in vitro* than *in vivo* suggest that some mechanisms compensating for the lack of sPLA$_2$-IIF might exist *in vivo*.

Strikingly, under pathological conditions, *Pla2g2f*$^{-/-}$ mice are protected from epidermal hyperplasia in models of Th17-dependent psoriasis and Th1-dependent CHS [45]. In primary keratinocytes from *Pla2g2f*$^{-/-}$ mice, IL-22- or IL-17A-induced expression of several psoriasis markers is markedly impaired. Mechanistically, sPLA$_2$-IIF hydrolyzes P-PE secreted from keratinocytes to yield P-LPE, a unique lysophospholipid that facilitates the differentiation and activation of keratinocytes, leading to the propagation of skin inflammation. Indeed, the levels of P-LPE in the skin are correlated well with the expression levels of sPLA$_2$-IIF in multiple skin disease models, and topical application of P-LPE to *Pla2g2f*$^{-/-}$ skin *in vivo* or supplementation of *Pla2g2f*$^{-/-}$ keratinocytes with P-LPE *ex vivo* restores the psoriasis-related phenotypes. Thus, in the pathology of psoriasis, sPLA$_2$-IIF plays an exacerbating role by promoting aberrant proliferation and activation of keratinocytes through production of P-LPE in the suprabasal epidermis, whereas sPLA$_2$-IID plays a resolving role by reducing the harmful Th17 immune response through production of ω3 PUFA-derived pro-resolving mediators in lymphoid tissues (see above) (Fig. 3A).

4.3. Skin cancer

Skin-specific *Pla2g2a*-TG mice are sensitive to chemical carcinogenesis [82], even though endogenous sPLA$_2$-IIA is not expressed in mouse skin. Likewise, *Pla2g2f*-TG mice are highly susceptible to the skin carcinogenesis model, with an apparent propensity to develop larger tumors than WT mice [45], implying again that the overexpressed sPLA$_2$-IIA in *Pla2g2a*-TG mice mimics the action of sPLA$_2$-IIF. Importantly, *Pla2g2f*$^{-/-}$ mice on a BALB/c background are markedly protected from the development of skin tumors, accompanied by lower production of P-LPE and unaltered production of canonical AA metabolites [45]. Among the sPLA$_2$ knockout mouse strains tested so far, only *Pla2g2d*$^{-/-}$ and *Pla2g2f*$^{-/-}$ mice are protected against skin cancer through distinct mechanisms; sPLA$_2$-IID deficiency increases anti-tumor immunity and thereby blocks tumor development (see above), whereas sPLA$_2$-IIF deficiency ameliorates keratinocyte hyperproliferation (Fig. 3B) [31,45].

Taken together, the findings so far suggest that sPLA$_2$-IIF promotes epidermal hyperplasic diseases including psoriasis and skin cancer and that P-LPE, a primary sPLA$_2$-IIF product, represents a particular biomarker and bioactive lipid that reflects the expression and function of sPLA$_2$-IIF. Given that sPLA$_2$-IIF is expressed in the epidermis rather specifically and that *Pla2g2f*$^{-/-}$ mice display more profound skin phenotypes under pathological conditions than under physiological conditions, blocking or neutralizing this particular sPLA$_2$ may be a novel approach for specific treatment of psoriasis, skin cancer, or other conditions characterized by epidermal hyperplasia. It remains to be clarified whether sPLA$_2$-IIF-driven P-LPE would act on keratinocytes through a specific receptor or through other mechanism(s), and whether DHA, another sPLA$_2$-IIF-driven product, would be metabolized to certain products that would affect skin homeostasis. The latter possibility seems plausible, since DHA and its metabolites have been shown to have the capacity to facilitate skin wound healing, suppress psoriasis, and prevent neoplastic transformation of keratinocytes [84–86].

4.4. Other potential functions

Recombinant sPLA$_2$-IIF has a potent capacity to prevent malaria infection *in vitro* [87]. The anti-malaria property of sPLA$_2$s is dependent on their ability to release PUFAs relative to other fatty acids from lipoproteins, sPLA$_2$-IIF being the most PUFA-selective sPLA$_2$. Indeed, lipoprotein phospholipids are potently hydrolyzed, with marked PUFA preference, when treated with sPLA$_2$-IIF *in vitro* [87,88] or in *Pla2g2f*-TG mice *in vivo* (Fig. 3C). Beyond this ability to confer anti-malaria immunity, lipoprotein hydrolysis by sPLA$_2$s would be expected to have some influence on systemic metabolism, as has been demonstrated for the “metabolic sPLA$_2$s” sPLA$_2$-IIE and -V (see above) [62]. In this context, it would be important to determine whether endogenous sPLA$_2$-IIF has an opportunity to encounter plasma lipoproteins under certain *in vivo* conditions, and if so, which cells or tissues would secrete sPLA$_2$-IIF in this context and how sPLA$_2$-IIF-directed lipoprotein hydrolysis would affect immunity or metabolism. Although sPLA$_2$-IIF is also substantially expressed in the intestinal epithelium [45], its deficiency does not significantly alter the sensitivity to colitis in an animal model [44].

5. sPLA$_2$-III

5.1. General aspects

Human sPLA$_2$-III was originally identified by Lambeau and his colleagues in 2000 [19]. sPLA$_2$-III is an atypical sPLA$_2$ whose structure is rather distinct from conventional group I/II/V/X sPLA$_2$s except for the conserved catalytic site and the Ca^{2+}-binding motif. Human sPLA$_2$-III has 490 amino acids made up of a central sPLA$_2$ domain (141 residues) with a typical group III feature that is flanked by unique N- and C-terminal domains (130 and 219 residues, respectively), and its gene maps to chromosome 22q. The central sPLA$_2$ domain is similar to bee venom sPLA$_2$ and possesses all of the features of group III sPLA$_2$s including 10 cysteines. Unlike sPLA$_2$-IB and -X, in which the N-terminal propeptide interferes with catalytic activity, the presence of the N- and C-terminal domains does not profoundly affect the activity of sPLA$_2$-III [19,89]. Molecular modeling of the sPLA$_2$ domain has revealed that sPLA$_2$-III has unique structural features in comparison with conventional sPLA$_2$s, such as a decrease in the volume of the substrate-binding hydrophobic channel [90].

When overexpressed in HEK293 cells or primary fibroblasts, sPLA$_2$-III elicits AA release with a potency comparable to that of sPLA$_2$-IIF and

superior to that of sPLA$_2$-IIA [24,89]. The N- and C-terminal domains are removed to give rise to a mature, sPLA$_2$ domain-only form [91]. Overexpressed sPLA$_2$-III in mammalian or insect cells is often *N*-glycosylated at two positions, which affect the secretion of the enzyme [91], although the *N*-glycosylation of endogenous sPLA$_2$-III has not yet been confirmed *in vivo*. Evaluation of the enzymatic property using a lipidomics-based natural membrane assay with a mixture of colon-extracted phospholipids as the substrate has demonstrated that sPLA$_2$-III hydrolyzes all phospholipid subclasses including PC, PE, PS, PI and PG (*i.e.* with no apparent polar head group specificity), tending to prefer the *sn*-2 position of PUFAs [92]. In mice, sPLA$_2$-III is distributed in several tissues, showing the highest expression in the colon, skin, and male reproductive organs [92,93]. Indeed, mice null for sPLA$_2$-III (*Pla2g3*$^{-/-}$) and those with transgenic overexpression of human sPLA$_2$-III (*PLA2G3*-TG) display several remarkable phenotypes in these tissues, as described below. Importantly, these studies have revealed that the same sPLA$_2$ may work in different tissues by different mechanisms for different biological effects.

5.2. Male reproduction

After the complex process of testicular germ cell differentiation, spermatozoa exit the seminiferous tubules of the testis into the epididymis. During the epididymal transit of spermatozoa, PC in the sperm membrane undergoes a dramatic shift in its *sn*-2 acyl groups from OA and AA to DHA and docosapentaenoic acid (DPA), and the increased proportion of DPA/DHA consequently contributes to increased sperm membrane fluidity, and thereby flagellar motility and oocyte fertilization [94–97]. The percentage of DHA relative to total fatty acids is correlated with the normal morphology and fertility of sperm cells [98]. Male hypofertility in *Pla2g3*$^{-/-}$ mice highlights a critical role of sPLA$_2$-III in this epididymal sperm maturation process [93]. In fact, when mutant males are mated with WT females, the litter sizes are reduced in a genotype-related manner, with only 2–3 pups per litter after breeding of *Pla2g3*$^{-/-}$ males with *Pla2g3*$^{+/+}$ females.

sPLA$_2$-III is expressed in epididymal epithelial cells as well as testicular Sertoli cells [93]. In the epididymis, sPLA$_2$-III is secreted from the epithelium into the lumen and acts on immature sperm cells passing through the duct in a paracrine manner to regulate phospholipid remodeling. Strikingly, sperm membrane phospholipid remodeling in the epididymis, but not testicular spermatogenesis, is severely compromised in *Pla2g3*$^{-/-}$ mice [93]. Accordingly, *Pla2g3*$^{-/-}$ spermatozoa, with a low proportion of DPA/DHA, have aberrant acrosomes and an abnormal axoneme configuration in flagella, resulting in reduced motility and fertility. Epididymal sPLA$_2$-III may participate in deacylation of OA and AA from sperm phospholipids, followed by reacylation with DHA and DPA by a certain lysophospholipid acyltransferase (possibly LPAAT3 [99]) leading to an increase of DPA/DHA-containing PC in mature sperm cells. In the *Pla2g3*$^{-/-}$ epididymis, impairment of the deacylation step may eventually perturb the subsequent reacylation with DPA/DHA, culminating in the asthenozoospermia phenotype.

In addition to *Pla2g3*$^{-/-}$ mice, sPLA$_2$-X-deficient (*Pla2g10*$^{-/-}$) mice also display sperm abnormality. In *Pla2g10*$^{-/-}$ mice, spermatogenesis and epididymal sperm maturation occur normally, but subsequent sperm activation including the acrosome reaction is impaired, thus affecting fertilization [44,100,101]. sPLA$_2$-X is secreted from the sperm acrosome and selectively hydrolyzes DPA/DHA-bearing PC species in sperm membranes to release DPA, DHA and LPC, among which DPA and to a lesser extent LPC can restore the fertilization capacity of *Pla2g10*$^{-/-}$ sperm [44]. Thus, sPLA$_2$-III promotes epididymal sperm maturation, allowing enrichment of DPA/DHA-containing PC species in sperm membranes, while sPLA$_2$-X acts on these DPA/DHA-rich phospholipids to liberate DPA and LPC for successful fertilization, thus underscoring elegant cooperation of these two “reproductive sPLA$_2$s” in the process of male reproduction. From a clinical standpoint, sPLA$_2$-III and -X are potential targets for the development of male contraceptive agents or as potential diagnostic markers of male sterility.

5.3. Anaphylaxis

It has been well established that cPLA$_2\alpha$ is essential for the production of PGD$_2$ and leukotrienes by mast cells, a key effector cell population in allergy [102,103]. Beyond this, the hypothesis that sPLA$_2$-III might participate in mast cell activation and allergy stemmed primarily from the fact that this enzyme is the sole mammalian homolog of bee venom sPLA$_2$, which is a potent mast cell activator and anaphylaxis inducer [19]. Indeed, like bee venom sPLA$_2$, exogenous human sPLA$_2$-III elicits mast cell activation when injected into mouse skin [34]. Endogenous sPLA$_2$-III is expressed in mouse and human mast cells, where it is stored in secretory granules and released upon cell activation. Detailed analysis of *Pla2g3*$^{-/-}$ mice has revealed that sPLA$_2$-III not merely acts as a mast cell activator, but also functions essentially as a regulator of mast cell maturation.

Microenvironmental alterations of mast cell phenotypes through intercellular communication with fibroblasts affect susceptibility to allergy [104,105]. However, the mechanisms underlying the maturation of mast cells toward an allergy-sensitive phenotype remain incompletely understood. Mast cell-dependent passive and active anaphylactic responses are markedly attenuated in *Pla2g3*$^{-/-}$ mice and conversely augmented in *PLA2G3*-TG mice in a cell-autonomous manner [34]. Skin mast cells in *Pla2g3*$^{-/-}$ mice are morphologically and functionally immature, with markedly lower histamine and protease contents in secretory granules, expression of mast cell maturation markers, and cell surface expression of FcεRI. Moreover, bone marrow-derived mast cells (a relatively immature mast cell population) prepared from *Pla2g3*$^{-/-}$ mice exhibit impaired fibroblast-driven maturation and thereby IgE-dependent and even -independent activation in *ex vivo* culture. Importantly, similar mast cell abnormalities are also evident in mice lacking lipocalin-type PGD$_2$ synthase (L-PGDS) or those lacking the PGD$_2$ receptor DP1 [34]. Indeed, genetic or pharmacological inactivation of DP1 in mast cells or of L-PGDS in fibroblasts phenocopies that of sPLA$_2$-III in mast cells toward defective mast cell maturation and anaphylaxis.

Collectively, sPLA$_2$-III secreted from immature mast cells is functionally coupled with fibroblastic L-PGDS to provide a microenvironmental pool of PGD$_2$, which in turn acts on DP1 on mast cells to promote their appropriate maturation (Fig. 4A). This PGD$_2$-dependent paracrine circuit involving sPLA$_2$-III, L-PGDS and DP1 explains a missing link required for fibroblast-driven maturation of mast cells [106]. Accordingly, a new agent that specifically inhibits this unique sPLA$_2$ may be useful for the treatment of patients with mast cell-associated allergic and other diseases. It should be noted, however, that the mast cell defects observed in mice lacking sPLA$_2$-III tend to be more severe than those observed in mice lacking L-PGDS or DP1 [34], suggesting that the full maturation of mast cells may require an additional sPLA$_2$-III-driven lipid signal(s).

5.4. Colonic inflammation and cancer

Colorectal cancer is a frequent form of malignancy and a major cause of death in the Western hemisphere. Sporadic colon cancers exhibit some aspects of inflammation, and the pathogenesis of some types of colon cancer is associated with inflammatory bowel disease [107]. Several lines of evidence suggest a potential link between sPLA$_2$-III and the development of colon cancer. Implantation of sPLA$_2$-III-transfected colon cancer cells into nude mice leads to increased growth of tumor xenografts [91]. sPLA$_2$-III has been proposed as a candidate biomarker for human colon cancer [108]. Higher expression of sPLA$_2$-III in human colorectal cancer is positively correlated with a higher rate of lymph node metastasis and shorter survival [109]. Moreover, polymorphisms in the human sPLA$_2$-III gene (*PLA2G3*) are significantly associated with a higher risk of colorectal cancer [110]. Importantly, a recent study has

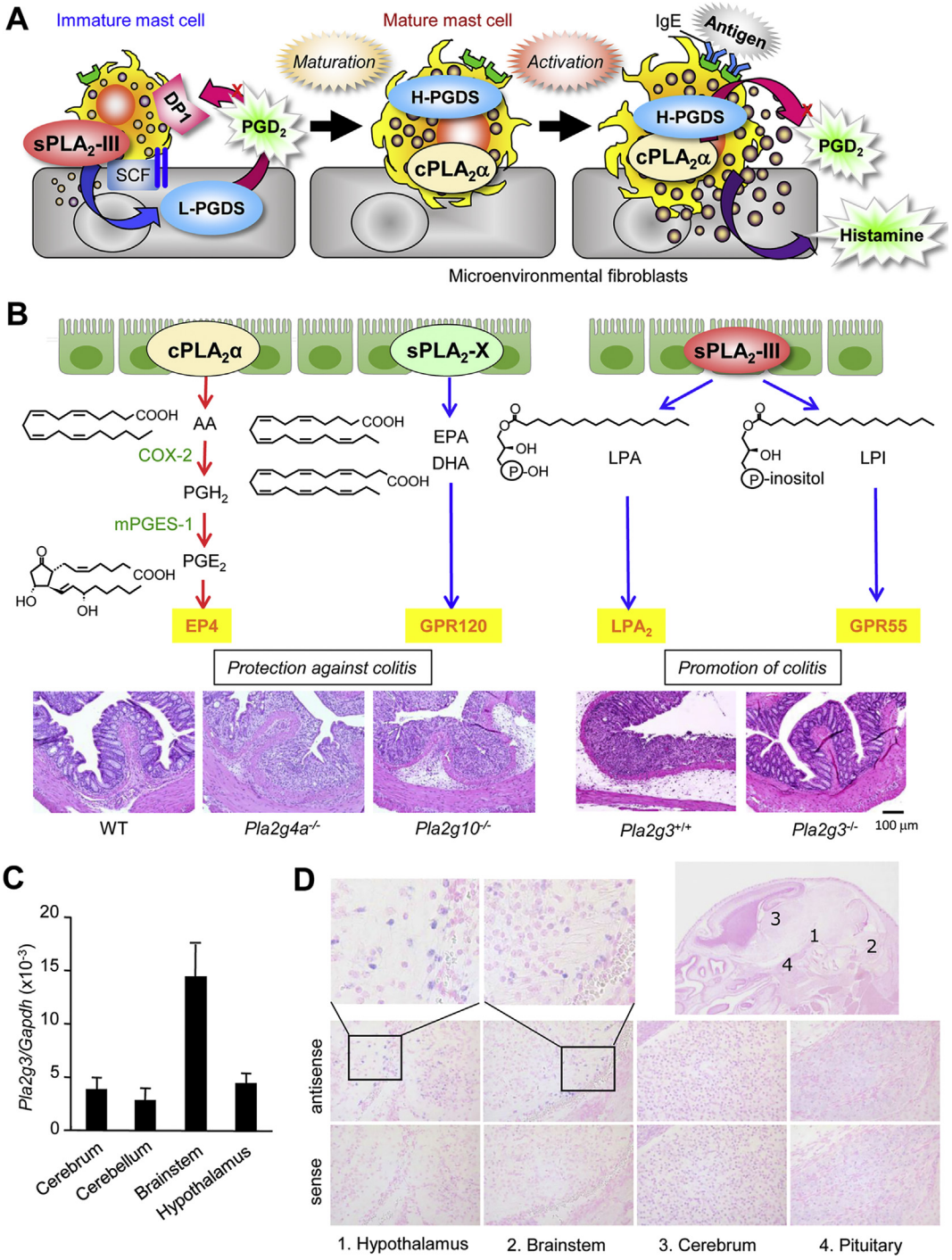

Fig. 4. Properties and functions of $sPLA_2$-III. (A) The role of $sPLA_2$-III in mast cell maturation and allergy [34]. $sPLA_2$-III is released from immature mast cells and coupled with fibroblastic L-PGDS to produce a microenvironmental pool of PGD_2, which in turn acts on DP1 to promote mast cell maturation. Mature mast cells, which express $cPLA_2\alpha$ and hematopoietic PGD_2 synthase (H-PGDS) abundantly, release a distinct pool of PGD_2 as well as histamine following activation by IgE and antigen, leading to allergic responses. Disturbance of the paracrine $sPLA_2$-III-L-PGDS-DP1 circuit hampers the maturation and thereby activation of mast cells, resulting in impairment of allergic responses. (B) The roles of distinct PLA_2s in the colon [44,92]. $cPLA_2\alpha$ releases a pool of AA that is converted to PGH_2 by cyclooxygenase-2 (COX-2) and then to PGE_2 by microsomal PGE_2 synthase (mPGES-1). This $cPLA_2\alpha$-driven PGE_2 confers protection from colitis through its receptor EP4 [143]. $sPLA_2$-X releases ω3 EPA/DHA, which blocks harmful Th17 responses in colitis through the PUFA receptor GPR120. In contrast, $sPLA_2$-III supplies lysophospholipids such as LPA and LPI, which promote colitis and colorectal cancer probably through their receptors LPA_2 and GPR55, respectively. Representative images of the colons of WT, *Pla2g4a*$^{-/-}$ and *Pla2g10*$^{-/-}$ mice treated with 1% DSS and those of *Pla2g3*$^{+/+}$ and *Pla2g3*$^{-/-}$ mice treated with 1.5% DSS are shown. (C) Real-time PCR of *Pla2g3* mRNA in the brain of 8-week-old C57BL/6 mice (n = 4, mean ± SEM). These results agree with a previous report [125]. (D) *In situ* hybridization of *Pla2g3* mRNA in the brain of newborn C57BL/6 mice. Signals for *Pla2g3* mRNA (blue) are located in several neurons within the hypothalamus and brainstem.

shown that sPLA$_2$-III is expressed in colonic epithelial cells and that its genetic deletion protects against colon cancer and colitis [92].

Pla2g3$^{-/-}$ mice are resistant to three distinct models of colon cancer, including those induced by azoxymethane (a model of carcinogen-induced cancer), by azoxymethane plus chronic treatment with dextran sulfate sodium (DSS) (a model of colitis-induced cancer), and by an APC mutation (*Apc*$^{Min/+}$; a model of familial adenomatous polyposis) [92]. Furthermore, *Pla2g3*$^{-/-}$ mice are less susceptible to DSS-induced acute colitis, with lower expression of pro-inflammatory and pathogenic Th17 cytokines and higher expression of epithelial barrier genes, than are *Pla2g3*$^{+/+}$ mice [92], implying that the amelioration of colonic inflammation by sPLA$_2$-III ablation underlies the protection against colon cancer (Fig. 4B). Lipidomics analysis has revealed that the *Pla2g3*$^{-/-}$ colon displays significant reduction of LPA and LPI species [92], which promote colon inflammation or cancer through their receptors LPA$_2$ and GPR55, respectively [111,112]. Production of these lysophospholipids by sPLA$_2$-III is evident in DSS-treated, but not in steady-state, colon, suggesting that sPLA$_2$-III acts on labile or damaged epithelial membranes in this disease setting. The colonic action of sPLA$_2$-III appears to be distinct from those of cPLA$_2$α and sPLA$_2$-X, which mobilize colon-protective PGE$_2$ and ω3 PUFAs, respectively, in the colon and thereby protect against colitis [44] (Fig. 4B). Overall, these results establish a role for sPLA$_2$-III in the aggravation of colonic inflammation and cancer, expand our understanding of the divergent roles of multiple PLA$_2$ enzymes in the colon, and point to sPLA$_2$-III as a novel druggable target for colorectal diseases.

5.5. Atherosclerosis

Clinically, an elevated plasma level of sPLA$_2$-IIA is an independent risk factor for cardiovascular disease [113]. It has been proposed that sPLA$_2$-mediated hydrolysis of lipoprotein phospholipids gives rise to a type of pro-atherogenic, small-dense LDL with an increased net negative charge, LPC content and aggregation propensity, as well as modified HDL whose anti-atherogenic function is decreased [114]. Indeed, LDL treated with several sPLA$_2$s such as sPLA$_2$-III, -V and -X facilitates the formation of lipid-laden foam cells from macrophages, a hallmark feature of atherosclerosis, *in vitro* [115,116]. On the basis of these backgrounds, the roles of conventional group I/II/V/X sPLA$_2$s in atherosclerosis have been investigated using their transgenic or knockout mice in several studies, although the results have been controversial [117–121]. Although varespladib, a pan-sPLA$_2$ inhibitor that broadly inhibits conventional group I/II/V/X sPLA$_2$s, prevented the development of atherosclerosis in animal studies [122], a phase III clinical trial using this compound failed to demonstrate its therapeutic efficacy in patients with cardiovascular disease [123]. This is likely because any advantageous effect of the inhibition of pro-atherogenic sPLA$_2$s would be cancelled out by the detrimental effect of the inhibition of anti-atherogenic sPLA$_2$s.

PLA2G3-TG mice crossed with *ApoE*$^{-/-}$ mice, followed by supplementation with an atherogenic diet, develop more advanced atherosclerotic lesions than *ApoE*$^{-/-}$ mice, accompanied by marked increases in pro-atherogenic LPC-rich small-dense LDL and the pro-thrombotic AA metabolite thromboxane (TX) A$_2$ [116]. *PLA2G3*-TG mice also develop systemic inflammation with increased age [124], suggesting that the elevated systemic inflammatory state may have an additional impact on promotion of atherosclerosis in these mice. Given that sPLA$_2$-III is insensitive to pan-sPLA$_2$ inhibitors, a new agent that targets this atypical sPLA$_2$ might be useful for treatment of atherosclerosis. Nonetheless, although the analysis of *PLA2G3*-TG mice has revealed the pro-atherogenic potential of sPLA$_2$-III, the definitive role of endogenous sPLA$_2$-III in atherosclerosis awaits further clarification using *Pla2g3*$^{-/-}$ mice.

5.6. Other potential roles

sPLA$_2$-III is expressed in the central nervous system, where it is distributed in the brainstem, hypothalamus, spinal cord, and cerebral neocortex (Fig. 4C, D) [125]. The localization of sPLA$_2$-III in dendrites or dendritic spines as well as postsynaptic structures in rat spinal cord suggests a potential role of this enzyme in neurotransmission or synaptic plasticity. In culture, sPLA$_2$-III can promote neuronal outgrowth and survival [126]. In humans, *PLA2G3* polymorphisms are associated with Alzheimer's disease [127]. The potential roles of sPLA$_2$-III in neuronal function and diseases need to be evaluated using *Pla2g3*$^{-/-}$ mice in future studies.

Interestingly, functional genomic screening has identified sPLA$_2$-III as a negative regulator of ciliogenesis [128] The primary cilium is a microtubule-based organelle that projects from the cell surface and acts as an antenna to sense extracellular cues and regulate diverse signaling pathways [129,130]. Defective cilium formation is associated with many pathologic states, including classical ciliopathies, obesity and cancer [131,132]. Using a *Pla2g3* knockdown strategy, it has been proposed that the production of lysophospholipids by sPLA$_2$-III, whose expression is controlled by the transcription factor SREBP-1c, disturbs endosomal recycling and vesicular trafficking toward normal ciliogenesis [133]. Therefore, the functions of sPLA$_2$-III in inflammation, cancer, and sperm flagellar motility (see above) might rely, at least in part, on the regulation of ciliogenesis by this enzyme.

6. Other poorly characterized sPLA$_2$s

sPLA$_2$-IIC has the structural features of group II sPLA$_2$s, but possesses an extra sequence in the middle region, thus having 16 cysteines (*i.e.* 8 disulfides) [134]. Although sPLA$_2$-IIC is expressed abundantly in meiotic cells in rodent testis [135], it is a pseudogene in humans [134]. Therefore, analysis of *Pla2g2c*$^{-/-}$ mice has not been performed. A cell biological study using *Pla2g2c* knockdown has shown that sPLA$_2$-IIC is up-regulated in hepatitis B-infected hepatocytes to produce LPE, which is then presented to CD1d on natural killer T cells, leading to propagation of an anti-virus immune response [136].

The atypical group XII subfamily contains two isoforms, sPLA$_2$-XIIA and -XIIB. The *in vivo* functions of sPLA$_2$-XIIA are largely obscure, since studies using *Pla2g12a*$^{-/-}$ mice have not yet been reported. sPLA$_2$-XIIA kills Gram-negative bacteria such as *Helicobacter pylori* even more efficiently than sPLA$_2$-IIA, a “bactericidal sPLA$_2$”, *in vitro* [137,138]. Forcible overexpression of sPLA$_2$-XIIA in *Xenopus laevis* embryos facilitates olfactory sensory neurogenesis [139]. sPLA$_2$-XIIA is present in axon terminals and dendrites in rat brain, and injection of its antisense oligonucleotide into the prefrontal cortex perturbs working memory and attention [140]. sPLA$_2$-XIIB, preferentially expressed in the liver, is catalytically inactive due to the replacement of the catalytic histidine by a leucine residue [141]. Mice lacking sPLA$_2$-XIIB (*Pla2g12b*$^{-/-}$) display steatohepatitis due to impaired hepatic secretion of very-low-density lipoprotein through an unknown, probably non-catalytic, mechanism [142].

7. Concluding remarks

Studies during the last decade have revealed the pathophysiological functions of various sPLA$_2$s, among which sPLA$_2$-IID, -IIE, -IIF and -III are highlighted in this review. It is now clear that individual sPLA$_2$s play unique and tissue-specific roles by acting on extracellular phospholipids, which include adjacent cell membranes, non-cellular 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 (mostly C57BL/6) studies, it is important to translate these studies to humans with caution. Although current data obtained from the

knockout studies have suggested that individual sPLA$_2$s are functionally non-redundant in most cases, the possibility that some of the functions could be compensated if sPLA$_2$-IIA is normally expressed cannot be fully ruled out. Further analyses in this research field and their integration for therapeutic applications will benefit from advanced lipidomics that can monitor the sPLA$_2$-associated lipid metabolism occurring within specific tissue niches in more detail. Hopefully, the next decade will yield a comprehensive map of sPLA$_2$-driven lipid networks, allowing the development and therapeutic application of a new class of sPLA$_2$ inhibitors.

Transparency document

The Transparency document associated with this article can be found, in online version.

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