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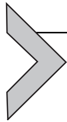

CHAPTER FOUR

The Roles of the Secreted Phospholipase A_2 Gene Family in Immunology

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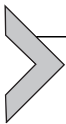
Abstract

Within the phospholipase A_2 (PLA_2) family that hydrolyzes phospholipids to yield fatty acids and lysophospholipids, secreted PLA_2 ($sPLA_2$) enzymes comprise the largest group containing 11 isoforms in mammals. Individual $sPLA_2$s exhibit unique tissue or cellular distributions and enzymatic properties, suggesting their distinct biological roles. Although PLA_2 enzymes, particularly cytosolic PLA_2 ($cPLA_2\alpha$), have long been implicated in inflammation by driving arachidonic acid metabolism, the precise biological roles of $sPLA_2$s have remained a mystery over the last few decades. Recent studies employing mice gene-manipulated for individual $sPLA_2$s, in combination with mass spectrometric lipidomics to identify their target substrates and products in vivo, have revealed their roles in diverse biological events, including immunity and associated disorders, through lipid mediator-dependent or -independent processes in given microenvironments. In this review, we summarize our current knowledge of the roles of $sPLA_2$s in various immune responses and associated diseases.



1. GENERAL ASPECTS OF $sPLA_2$s

PLA_2 enzymes are a group of enzymes that hydrolyze the *sn*-2 position of phospholipids to yield fatty acids and lysophospholipids (Fig. 1A). More than one-third of the PLA_2 enzymes belong to the $sPLA_2$ family, which contains 10 catalytically active isoforms (IB, IIA, IIC, IID, IIE, IIF, III, V, X, and XIIA) and 1 inactive isoform (XIIB) in mammals (Dennis, Cao, Hsu, Magrioti, & Kokotos, 2011; Lambeau & Gelb, 2008; Murakami, Sato, Miki, Yamamoto, & Taketomi, 2015; Murakami, Taketomi, Miki, et al., 2011). Conventional $sPLA_2$s (group I/II/V/X) are closely related 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 (groups III and XII) are each classified into distinct collections (Fig. 1B). Evolutionally, group IB $sPLA_2$ is the oldest conventional $sPLA_2$ in the animal kingdom since three IB-like genes are present in *C. elegans*, while group II, V, and X $sPLA_2$s exist only in vertebrates (Murakami, Taketomi, Miki, et al., 2011). Group III $sPLA_2$ is present in vertebrates and insects. The conservation of group XII $sPLA_2$s from bacteria to humans suggests that they emerged early in evolution prior to Eubacteria (Nevalainen & Cardoso, 2012). Group IX, XI,

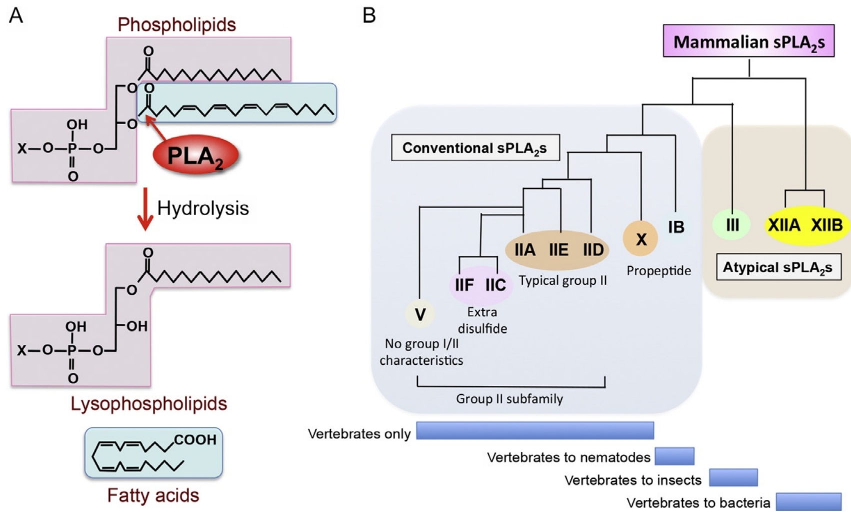


Fig. 1 PLA_2 reaction and mammalian $sPLA_2$ family. (A) PLA_2 reaction. (B) The phylogenetic tree of mammalian $sPLA_2$s. For details, see the text.

XIII, and XIV sPLA$_2$s are present in invertebrates, plants, viruses, and fungi, respectively, but not in vertebrates. The tissue or cellular distributions and stimulus inducibility of individual sPLA$_2$s are distinct (Fig. 2), suggesting their different biological roles. As sPLA$_2$s are secreted and require millimolar Ca^{2+} for their catalysis, they act essentially on extracellular phospholipids, including those in adjacent cell membranes, microparticles, surfactant, lipoproteins, and foreign lipids in foods or microorganisms, in response to microenvironmental cues.

Biochemical analyses have shown that individual sPLA$_2$s have distinct substrate selectivity in terms of polar head groups or *sn*-2 fatty acids of phospholipids. With regard to polar head groups, PLA2G2A and other group II sPLA$_2$s show preference for phosphatidylethanolamine (PE) over phosphatidylcholine (PC), while PLA2G10 is very active on PC, and these preferences can be partly explained in terms of crystal structure (Pan et al., 2002; Scott et al., 1991). With regard to *sn*-2 fatty acids, PLA2G1B, PLA2G2A, and PLA2G2E do not distinguish fatty acid species, PLA2G5 prefers fatty acids with a lower degree of unsaturation (eg, oleic acid (OA)), and PLA2G2D, PLA2G2F, PLA2G3, and PLA2G10 show preference for polyunsaturated fatty acids (PUFAs) such as arachidonic acid (AA) and docosahexaenoic acid (DHA) to various degrees (Chen & Dennis, 1998; Chen, Engle, Seilhamer, & Tischfield, 1994b; Cupillard, Koumanov,

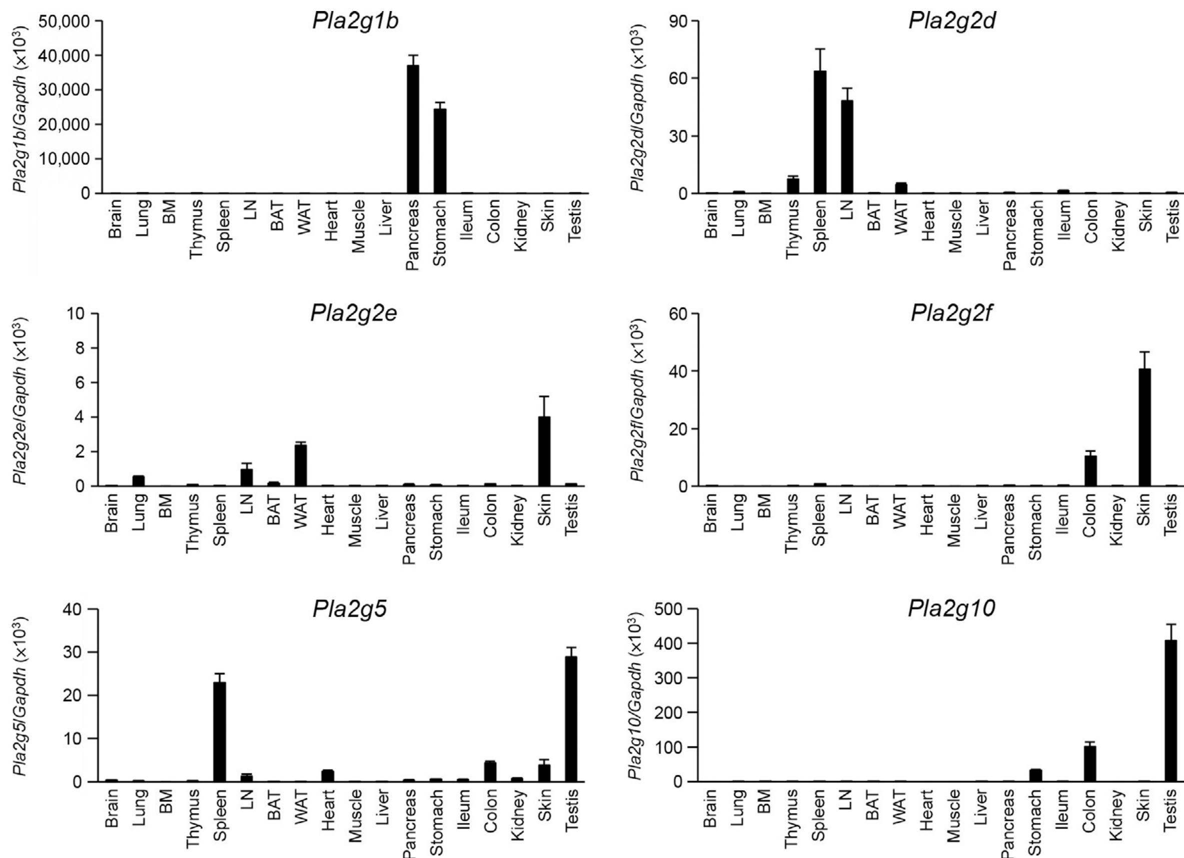
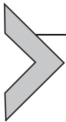


Fig. 2 Tissue distribution of sPLA$_2$s. Expression profiles of sPLA$_2$s in various tissues of 10-week-old male C57BL/6 mice, as assessed by real-time PCR ($n = 4$–8). Values are mean ± SEM.

Mattei, Lazdunski, & Lambeau, 1997; Guillaume et al., 2015; Hanasaki et al., 1999; Miki et al., 2013; Mitsuishi, Masuda, Kudo, & Murakami, 2007; Murakami et al., 2003; Murase et al., 2016; Pruzanski et al., 2005; Sato et al., 2014; Yamamoto et al., 2015). Although the substrate specificity of $sPLA_2s$ differs according to the in vitro assay conditions employed, particularly when excess amounts of the enzymes are used, the overall tendency is recapitulated in several if not all in vivo systems, often with even more selective patterns of hydrolysis that may be affected by the phospholipid compositions of the target membranes. The classification, biochemical, and cell biological features of $sPLA_2s$ have been detailed in other recent reviews (Dennis et al., 2011; Lambeau & Gelb, 2008; Murakami & Lambeau, 2013; Murakami et al., 2015; Murakami, Taketomi, Girard, Yamamoto, & Lambeau, 2010; Murakami, Taketomi, Miki, et al., 2011; Murakami et al., 2014; Murakami, Taketomi, Sato, & Yamamoto, 2011). In this chapter, we highlight the in vivo functions and associated lipid-metabolic actions of $sPLA_2s$ in the context of immunity and related diseases as revealed by studies using transgenic (TG) and/or knockout (KO) mice in combination with sophisticated lipidomics approaches to reveal their in vivo lipid substrates and metabolites.

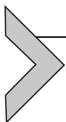


2. POTENTIAL ROLES OF $sPLA_2s$: LESSONS FROM $sPLA_2$ TRANSGENIC MICE

Some of the biological actions of $sPLA_2s$ in vivo have been addressed using $sPLA_2$-overexpressing TG mice, which have provided informative insights into the potential pathophysiological roles of $sPLA_2s$ (Ait-Oufella et al., 2013; Cash, Kuhel, Goodin, & Hui, 2011; Curfs et al., 2008; Grass et al., 1996; Ivandic et al., 1999; Laine, Grass, & Nevalainen, 1999; Mulherkar et al., 2003; Ohtsuki et al., 2006; Sato et al., 2011, 2008, 2009; Taketomi et al., 2013; Yamamoto et al., 2015, 2011). In this section, we briefly summarize general aspects, rather than describing individual topics in detail, of $sPLA_2$-TG mice. It is noteworthy that not all $sPLA_2$-TG mice develop inflammatory phenotypes, arguing against the current assumption that $sPLA_2s$ generally participate in inflammation by producing proinflammatory eicosanoids (ie, AA metabolites) including prostaglandins (PGs) and leukotrienes (LTs). More critically, the overall phenotypes of TG mice for different $sPLA_2s$ are not entirely identical. If different $sPLA_2s$ have similar enzymatic properties, then the resulting phenotypes of mice that are TG for them would be expected to be similar, but this is not actually the case.

The most likely explanation for this is that individual $sPLA_2$s have distinct enzymatic properties, acting on different phospholipid substrates and mobilizing different lipid metabolites in vivo. For instance, *Pla2g5*-TG mice display neonatal death due to lung collapse, whereas TG mice for other $sPLA_2$s do not show such a lethal phenotype (Grass et al., 1996; Ohtsuki et al., 2006; Sato et al., 2008; Yamamoto et al., 2015). This is likely because PLA2G5, compared with other $sPLA_2$s, is potently active on dipalmitoyl-PC, a major surfactant phospholipid, under in vivo conditions. If TG mice for a certain $sPLA_2$ display a particular phenotype opposite to that in KO mice deficient in the same $sPLA_2$, we can emphasize that this phenotype reflects the intrinsic function of the given $sPLA_2$. In this case, TG mice are useful for screening potential substrates and products driven by this enzyme in vivo, since lipid mobilizations in $sPLA_2$-TG mice are typically large and easy to monitor using lipidomics approaches. In subsequent sections, some examples of these findings will be presented.

However, the results obtained from TG mice should be interpreted with caution, since superphysiological levels of $sPLA_2$, even in tissues or cells where the enzyme is not expressed endogenously, could result in artificial phenotypes. An example is alopecia (hair loss) observed in *PLA2G2A*- or *PLA2G10*-TG mice (Grass et al., 1996; Yamamoto et al., 2011), despite the fact that endogenous expression of these $sPLA_2$s in mouse skin is very low or undetectable (Yamamoto et al., 2015). In fact, when artificially overexpressed in the skin, these $sPLA_2$s mimic the intrinsic actions of PLA2G2F, a major $sPLA_2$ endogenously expressed in the epidermis (see later). Furthermore, *PLA2G3*-TG mice exhibit a distinct skin phenotype manifested by age-associated spontaneous inflammation (Sato et al., 2009), whereas TG mice for other $sPLA_2$s do not show noticeable skin abnormality (unpublished results). These observations again imply that different $sPLA_2$s have distinct enzymatic properties, hydrolyzing different phospholipids to mobilize different lipid products in vivo.



3. GROUP IIA $sPLA_2$ (PLA2G2A)

PLA2G2A ($sPLA_2$-IIA) is a prototypic $sPLA_2$ whose levels in sera or inflammatory exudates are positively correlated with the severity of inflammatory diseases (eg, rheumatoid arthritis, sepsis, and cardiovascular diseases; Kugiyama et al., 1999; Pruzanski, Vadas, Stefanski, & Urowitz, 1985). Expression of this $sPLA_2$ isoform is markedly induced by proinflammatory stimuli such as LPS, IL-1β, and IFN-γ in a wide variety of cells and tissues in

various animal species including humans (Crowl, Stoller, Conroy, & Stoner, 1991; Kuwata, Nakatani, Murakami, & Kudo, 1998; Nakano, Ohara, Teraoka, & Arita, 1990). PLA2G2A is the only $sPLA_2$ isoform detected in the blood circulation, particularly under inflammatory conditions. In mice, however, its expression is highly restricted to the intestine (eg, BALB/c strain) or not expressed at all due to a natural frameshift mutation (eg, C57BL/6 and 129 strains; Kennedy et al., 1995; MacPhee et al., 1995). This situation hinders precise assessment of the physiological functions of PLA2G2A by the standard gene-targeting strategy, in which C57BL/6 and 129 strains are generally used. Therefore, until very recently, the in vivo functions of PLA2G2A have been addressed mainly using TG mice.

3.1 Antibacterial Defense

Because of its low affinity for PC as mentioned earlier, PLA2G2A hardly hydrolyzes phospholipids in quiescent mammalian cells by acting directly on the outer leaflet of the plasma membrane, which is PC rich. Instead, PLA2G2A efficiently hydrolyzes phospholipids in bacterial membranes, which are PE rich. Indeed, PLA2G2A kills bacteria (Gram-positive in particular) at physiological concentrations in vitro (Singer et al., 2002). In addition to this substrate preference, the highly cationic nature of PLA2G2A, which is not shared with other $sPLA_2s$, is also critical for bacterial killing by this enzyme (Koprivnjak, Peschel, Gelb, Liang, & Weiss, 2002; Weiss, Inada, Elsbach, & Crowl, 1994). Indeed, PLA2G2A is highly expressed in the exocrine glands such as intestinal Paneth cells and tear glands (Qu & Lehrer, 1998), which are continuously exposed to environmental bacteria. Moreover, *PLA2G2A*-TG mice, or WT mice treated with PLA2G2A, show resistance to sepsis or pneumonia following bacterial infection (Laine et al., 1999; Laine, Grass, & Nevalainen, 2000; Movert, Wu, Lambeau, Touqui, & Areschoug, 2011; Pernet et al., 2014; Piris-Gimenez et al., 2005). Hence, it is now generally accepted that PLA2G2A plays an important role in host defense as a "bactericidal $sPLA_2$." Some bacteria such as *Pseudomonas aeruginosa* and *Bacillus anthracis* can escape the bactericidal action of PLA2G2A by suppressing its induction in macrophages (Pernet et al., 2014; Raymond et al., 2007).

3.2 Inflammation

As PLA2G2A is released or induced by proinflammatory stimuli in various immune cells, it has been speculated that this $sPLA_2$ might play a role in inflammation, and yet definitive evidence for this hypothesis had been

lacking over the last few decades. A number of cell-based studies have shown that PLA2G2A, when overexpressed or added exogenously at high concentrations, is capable of releasing AA from cytokine-primed or apoptotic cells, in which its preferred substrate PE or phosphatidylserine (PS) might be exposed on the outer leaflet of the plasma membrane (Koduri et al., 2002; Murakami et al., 1998). However, it is unclear whether this system is in fact operative in vivo. Recently, the concept that PLA2G2A acts as a driver of sterile inflammation has been examined in a series of studies by Boilard and colleagues, who backcrossed the mutated *Pla2g2a* allele in the C57BL/6 strain onto the BALB/c strain to produce *Pla2g2a*$^{-/-}$ BALB/c mice. These *Pla2g2a*$^{-/-}$ mice are protected from autoantibody-induced arthritis, a model of rheumatoid arthritis, whereas *PLA2G2A*-TG mice are more susceptible to this arthritis model (Boilard et al., 2010). These complementary results obtained using KO and TG mice strongly support the proinflammatory role of PLA2G2A.

Furthermore, Boilard and colleagues have elegantly shown that PLA2G2A hydrolyzes phospholipids in microparticles, particularly in extracellular mitochondria (a type of organelle that evolutionally originated from bacteria), which are released from activated platelets or leukocytes at inflamed sites (Boudreau et al., 2014). Hydrolytic breakdown of mitochondrial or microparticular membranes by PLA2G2A gives rise to inflammatory mediators including eicosanoids and lysophospholipids, as well as mitochondrial DNA (DAMP; danger-associated molecular pattern), which promotes leukocyte activation. Moreover, PLA2G2A-targeted extracellular mitochondria or microparticles interact with neutrophils, allowing their adhesion to the vascular walls. Hydrolysis of microparticles by PLA2G2A results in the production of 12*S*-hydroxyeicosatetraenoic acid (HETE), an AA metabolite that acts on its receptor BLT2 to amplify cytokine production and cPLA$_2$α-dependent LTB$_4$ generation by neutrophils, thereby leading to acceleration of sterile inflammation (Duchez et al., 2015). These breakthrough findings account for a long-sought mechanism for the role of PLA2G2A as an "inflammatory sPLA$_2$." Thus, it is likely that PLA2G2A is primarily involved in host defense by killing bacteria and triggering innate immunity, whereas overamplification of the response leads to inflammation (Fig. 3).

3.3 Cancer

Chronic inflammation poses a potential risk for the development of cancer. PLA2G2A expression is correlated positively with prostate, lung, and breast

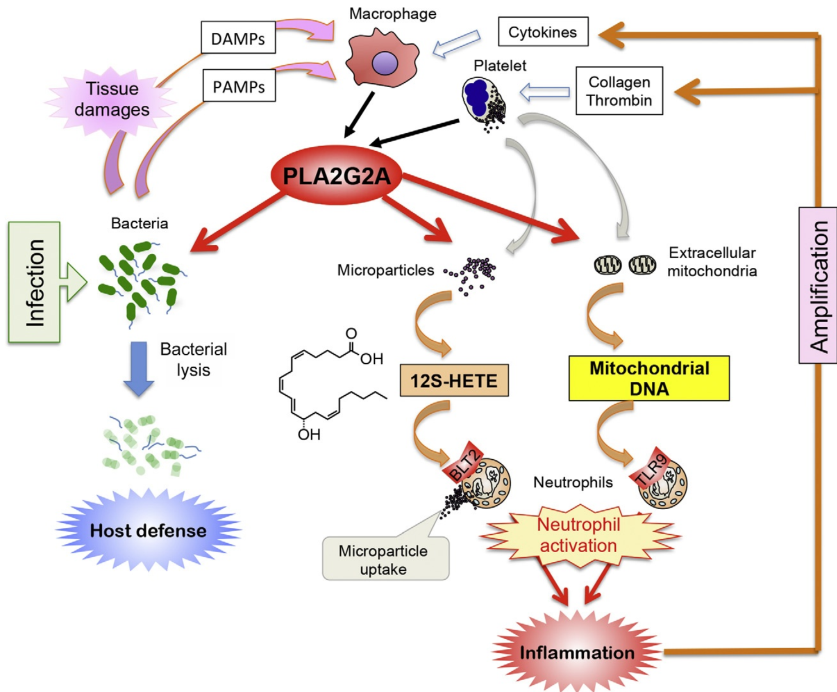


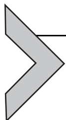
Fig. 3 Biological roles of PLA2G2A in host defense and inflammation. PLA2G2A, which is induced and secreted by immune cells (eg, macrophages and platelets) in response to proinflammatory stimuli (eg, pattern (PAMPs)- or danger (DAMPs)-associated molecular patterns), hydrolyzes bacterial membrane phospholipids to eliminate bacteria, thereby playing a key role in antibacterial host defense. PLA2G2A also contributes to augmented production of proinflammatory lipid mediators and cytokines by acting on phospholipids in microparticles or extracellular mitochondria, thereby amplifying inflammation.

cancers (Brglez, Lambeau, & Petan, 2014; Graff et al., 2001; Scott et al., 2010), in which chronic inflammation induced by PLA2G2A might contribute to the promotion of these cancers. Indeed, PGs and LTs, which are potential downstream lipid mediators of PLA$_2$s, are involved in cancer development (Chen, Hu, Zhang, Peng, & Li, 2009; Nakanishi et al., 2008). On the other hand, mouse strains intrinsically lacking PLA2G2A are more susceptible to intestinal tumorigenesis (MacPhee et al., 1995). TG expression of the intact *Pla2g2a* gene in C57BL/6 mice, a strain that has a mutated *Pla2g2a* allele, reverses this phenotype (Cormier et al., 1997), indicating that PLA2G2A has an antitumor effect in the gastrointestinal (GI) tract. Consistently, gene polymorphisms in the *PLA2G2A* gene are associated with

fundic gland polyposis in patients with familial adenomatous polyposis (Tomlinson, Beck, Neale, & Bodmer, 1996) and *PLA2G2A* expression is inversely correlated with the incidence of gastric cancer in humans (Leung et al., 2002). Although at present the mechanism underlying the antitumor role of PLA2G2A in the GI tract remains unclear, it is speculated that PLA2G2A, a "bactericidal $sPLA_2$," secreted from intestinal Paneth cells or colorectal epithelial cells may alter the intestinal microbiota, thereby affecting tumor development.

3.4 Atherosclerosis

Atherosclerosis is characterized by low-grade chronic inflammation in the arterial wall. PLA2G2A, as an "inflammatory $sPLA_2$," has long been believed to be a biomarker, and possibly an effector, for atherosclerosis, as the serum PLA2G2A levels show a positive correlation with cardiovascular disease (Kugiyama et al., 1999) and *PLA2G2A* gene polymorphisms are associated with atherosclerosis (Wootton et al., 2006). In support of this, *PLA2G2A*-TG mice or $Ldlr^{-/-}$ mice harboring adoptively transferred *PLA2G2A*-TG bone marrow cells develop advanced atherosclerotic lesions (Ivandic et al., 1999; Webb et al., 2003). However, since superphysiological levels of $sPLA_2$ in TG mice often result in artificial phenotypes as mentioned earlier, conclusive evidence for the aggravating role of PLA2G2A in atherosclerosis awaits future studies using $Pla2g2a^{-/-}$ mice on a suitable genetic background. We will discuss the potential roles of $sPLA_2$s in atherosclerosis again in subsequent sections.



4. GROUP IID $sPLA_2$ (PLA2G2D)

PLA2G2D ($sPLA_2$-IID), which is structurally most similar to PLA2G2A (Valentin, Koduri, et al., 1999), is expressed preferentially in secondary lymphoid organs such as the spleen and lymph nodes (LNs) (Fig. 2), where it is enriched in $CD11c^+$ dendritic cells (DCs; Miki et al., 2013). Among the DC subsets in lymphoid organs, PLA2G2D is expressed most abundantly in $CD4^+$ DCs, which assist humoral immunity in general. Albeit at lower levels, PLA2G2D is also expressed in tissue-resident DCs (eg, dermal and pulmonary DCs), $CD11b^+CD11c^+$ inflammatory DCs, and regulatory T cells (Miki et al., 2013; Vijay et al., 2015; von Allmen et al., 2009). PLA2G2D expression is decreased after DC activation (Miki et al., 2013). When phospholipids extracted from the LNs are used

as substrates, PLA2G2D preferentially hydrolyzes PE with AA and DHA, with a tendency to prefer the latter (Miki et al., 2013). These properties of PLA2G2D are consistent with its antiinflammatory role, as described later.

4.1 Contact Hypersensitivity

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, the resolution, but not propagation, of inflammation in the skin and LNs is delayed in *Pla2g2d*$^{-/-}$ mice (Miki et al., 2013). In the regional LNs, the levels of PUFAs including ω6 AA and ω3 DHA, as well as their antiinflammatory products including 15-deoxy-PGJ_2 and resolvin D1 (RvD1), respectively, are reduced in *Pla2g2d*$^{-/-}$ mice relative to WT mice, the reduction of the latter being more prominent (Fig. 4A). Together with its substrate selectivity as described earlier, PLA2G2D appears to preferentially hydrolyze AA- or DHA-bearing PE in LN membranes (likely microparticles), thereby mobilizing AA- or DHA-derived antiinflammatory lipid mediators (the latter in particular) that dampen Th1-driven adaptive immunity (Fig. 4B). Indeed, ω3 PUFA-derived resolvins suppress acquired immunity by dampening DC migration and antigen presentation to T cells (Sawada et al., 2015). Furthermore, administration of a PLA2G2D-Fc fusion protein to mice prevents experimental autoimmune encephalomyelitis and colitis (von Allmen et al., 2009). Thus, PLA2G2D is a "resolving $sPLA_2$" that ameliorates DC-committed innate and adaptive immune responses by mobilizing antiinflammatory lipid mediators. This is, to our knowledge, the first example of a particular $sPLA_2$ that mobilizes ω3 DHA and its metabolites in vivo.

4.2 Viral Infection

Oxidative stress and chronic low-grade inflammation in the lung are associated with aging and contribute to age-related immune dysfunction. PLA2G2D, whose expression in lung DCs increases with age in response to prolonged exposure to oxidative stress, contributes to worse outcomes in mice infected with severe acute respiratory syndrome-coronavirus or influenza virus (Vijay et al., 2015). *Pla2g2d*$^{-/-}$ mice are resistant to infection-induced death, accompanied by enhanced migration of lung

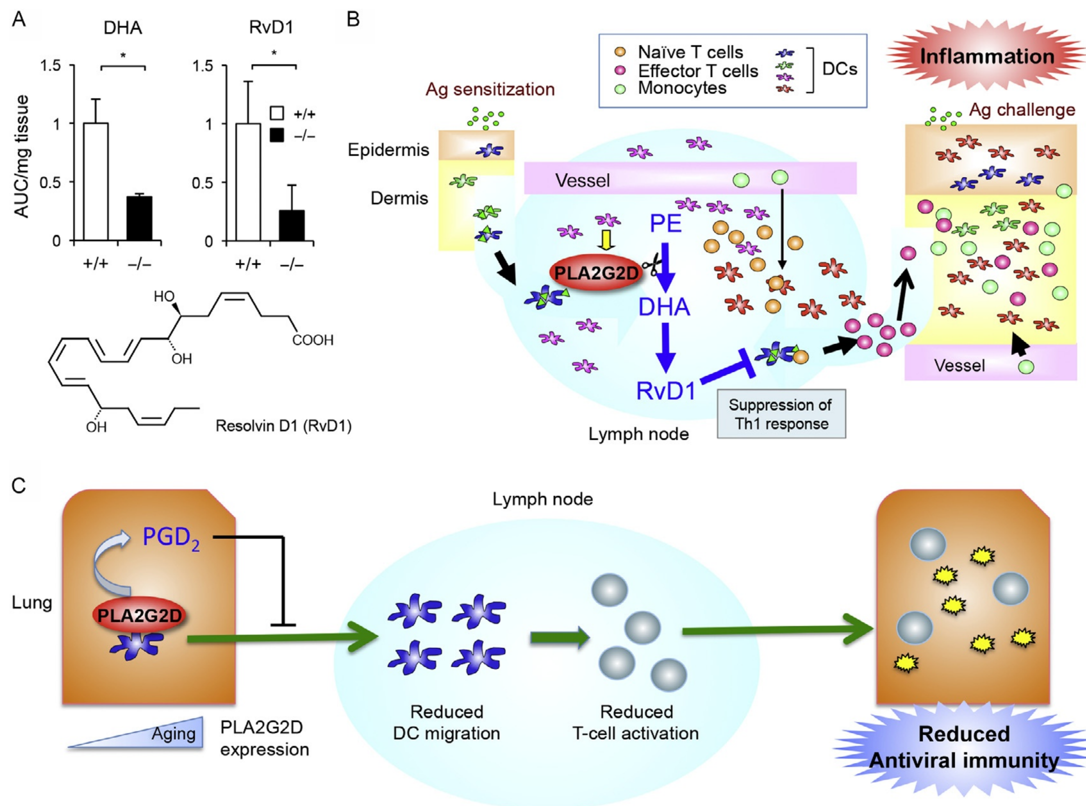
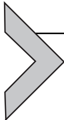


Fig. 4 Biological roles of PLA2G2D in antiinflammation. (A) Reduction of DHA and RvD1 levels in the draining LNs of *Pla2g2d*$^{-/-}$ mice compared to *Pla2g2d*$^{+/+}$ mice on 1 day after the second challenge of DNFB in the CHS model ($n=3$, mean ± SEM, $*P<0.05$). (B) A schematic model for the antiinflammatory role of PLA2G2D in CHS. PLA2G2D, which is expressed in DCs in the LNs, hydrolyzes PE to release PUFAs, particularly DHA, which is then metabolized to RvD1 that blocks the proinflammatory Th1 immune response. *Ag*, antigen. (C) Role of PLA2G2D in antiviral immunity. PLA2G2D in lung DCs produces PGD_2, which prevents DC migration into LNs and thereby suppresses T-cell activation. Accordingly, PLA2G2D attenuates antiviral immunity and increases viral infection.

DCs to draining LNs, augmented antivirus T-cell responses, and decreased lung injury. In this case, PLA2G2D is responsible for the pulmonary mobilization of PGD_2, which, by acting on its antiinflammatory receptor DP1, dampens DC migration and thereby T-cell-driven antivirus responses (Fig. 4C). Accordingly, the attenuated antiviral immunity in *Pla2g2d*$^{-/-}$ mice results in severe lung inflammation and early death. Thus, directed inhibition of PLA2G2D in the lungs of older patients with severe respiratory infections would be a potentially attractive therapeutic intervention for restoration of immune function.



5. GROUP IIF $sPLA_2$ (PLA2G2F)

PLA2G2F ($sPLA_2$-IIF) has structural features of group II $sPLA_2$, but possesses an extra C-terminal sequence with a unique Cys residue (Valentin, Ghomashchi, Gelb, Lazdunski, & Lambeau, 1999). Unlike other $sPLA_2$s which are active at neutral to alkaline pH ranges, PLA2G2F is fully active at mildly acidic pH. This property appears to be important for the role of PLA2G2F in the mildly acidic environment of the suprabasal epidermis, where this $sPLA_2$ is expressed predominantly (Fig. 2) (Ilic, Bollinger, Gelb, & Mauro, 2014; Yamamoto et al., 2015). PLA2G2F selectively hydrolyzes DHA-containing plasmalogen-PE (P-PE) in skin-extracted phospholipids to yield DHA and plasmalogen-lysophosphatidylethanolamine (P-LPE) at a physiological concentration (Yamamoto et al., 2015). PLA2G2F also hydrolyzes lipoprotein phospholipids to release PUFAs in vitro, which in turn prevent the in vitro growth of the malaria parasite (*Plasmodium falciparum*) in infected erythrocytes (Guillaume et al., 2015). However, the lipoprotein-hydrolytic and antimalaria actions of PLA2G2F need to be confirmed in vivo.

5.1 Psoriasis

PLA2G2F is expressed in terminally differentiated keratinocytes in the suprabasal epidermis and markedly increased in the hyperplasic epidermis of mice with skin disease models or patients with psoriasis (Yamamoto et al., 2015). Global or skin-specific *Pla2g2f*-TG mice spontaneously develop epidermal hyperplasia and alopecia, with increased expression of several psoriasis markers such as S100A9 (Fig. 5A). Although *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, primary keratinocytes isolated from the null mice show defective Ca^{2+}-induced differentiation and activation (Yamamoto et al., 2015).

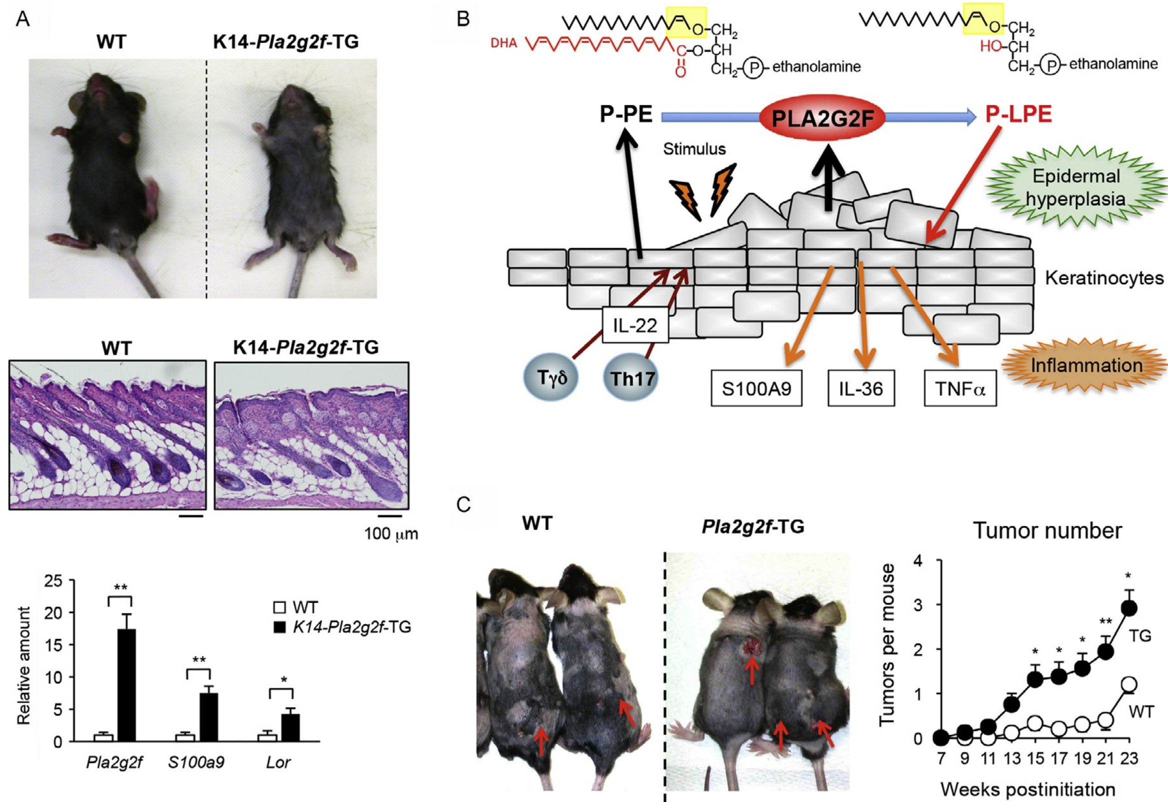
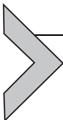


Fig. 5 Biological roles of PLA2G2F in epidermal hyperplasia. (A) Skin abnormalities in skin-specific (*K14*-) *Pla2g2f*-TG mice. Gross appearance (abdominal side; *top*) and skin histology as stained with hematoxylin and eosin (dorsal skin; *middle*) show that *K14-Pla2g2f*-TG mice spontaneously develop psoriasis-like epidermal hyperplasia with hair loss. Skin expression of psoriasis-associated genes is markedly increased in the TG skin compared to WT skin ($n = 4$; *bottom*). (B) A schematic model for the role of PLA2G2F in psoriasis. PLA2G2F, which is induced by IL-22 from Tγδ or Th17 cells, hydrolyzes extracellular P-PE released from keratinocytes to give rise to P-LPE, which then promotes keratinocyte activation leading to psoriatic epidermal hyperplasia and inflammation. (C) Aggravated skin cancer in *Pla2g2f*-TG mice in a carcinogenesis model. Gross appearance (*left*) and monitoring of tumor number ($n = 10$; *right*) in WT and TG mice are shown. Mean ± SEM, $^{*}P < 0.05$, $^{**}P < 0.01$.

The importance of PLA2G2F in skin pathophysiology has been highlighted in *Pla2g2f*$^{-/-}$ mice subjected to skin disease models (Yamamoto et al., 2015). Psoriasis is one of the most 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 infiltration and activation of immune cells such as Th17 cytokine-producing lymphocytes (Lowes, Suarez-Farinas, & Krueger, 2014). Strikingly, *Pla2g2f*$^{-/-}$ mice are protected from epidermal hyperplasia in models of Th17-dependent psoriasis and Th1-dependent CHS (Yamamoto et al., 2015). In the former model, PLA2G2F expression in keratinocytes is upregulated by IL-22 and to a lesser extent by IL-17A. In *Pla2g2f*$^{-/-}$ primary keratinocytes, IL-22- or IL-17A-induced expression of several psoriasis markers such as S100A9 and IL-36 is markedly impaired. Mechanistically, PLA2G2F hydrolyzes P-PE secreted from keratinocytes to yield P-LPE, a unique lysophospholipid that accelerates the differentiation and activation of keratinocytes, leading to propagation of skin inflammation (Fig. 5B). This finding provides the first in vivo evidence that a particular $sPLA_2$ regulates a biological process by mobilizing a lysophospholipid mediator.

5.2 Skin Cancer

Skin-specific *Pla2g2a*-TG mice are sensitive to chemical carcinogenesis (Mulherkar et al., 2003), although PLA2G2A is not expressed endogenously in mouse skin. *Pla2g2f*-TG mice are also more susceptible to the skin carcinogenesis model, with an apparent propensity to develop larger tumors than WT mice (Fig. 5C). Conversely, *Pla2g2f*$^{-/-}$ mice are highly protected from the development of skin tumors, accompanied by lower production of P-LPE and unaltered production of canonical AA metabolites (Yamamoto et al., 2015). Collectively, these results highlight the facts that PLA2G2F is a bona fide "epidermal $sPLA_2$" that promotes skin inflammation and cancer, that P-LPE is a biomarker and bioactive lipid that reflects the expression and function of PLA2G2F, and that PLA2G2A, when artificially overexpressed in mouse skin, may mimic the intrinsic pathological actions of PLA2G2F.



6. GROUP III $sPLA_2$ (PLA2G3)

PLA2G3 ($sPLA_2$-III), an atypical $sPLA_2$ that is more similar to bee venom group III $sPLA_2$ than to other mammalian $sPLA_2s$, has a central $sPLA_2$ domain with a typical group III feature that is flanked by unique

N- and C-terminal domains (Valentin, Ghomashchi, Gelb, Lazdunski, & Lambeau, 2000). The N- and C-terminal domains are removed to give rise to a mature, $sPLA_2$ domain-only form (Murakami et al., 2005). PLA2G3 does not discriminate the phospholipid polar head groups and *sn*-2 fatty acids, with a modest tendency to prefer PUFAs including linoleic acid (LA), AA, and DHA. PLA2G3 is able to augment the release of AA from transfected cells (Murakami et al., 2003) and lipoproteins (Sato et al., 2008) much more efficiently than can group II $sPLA_2$ members in vitro. Some of these properties might be related to the roles of this atypical $sPLA_2$ in vivo, as described later.

6.1 Anaphylaxis

Mast cells are known for their plasticity, and environmentally induced alterations in mast cell phenotypes could affect the severity of immediate hypersensitivity or anaphylaxis (Gurish & Austen, 2012; Rivera, Fierro, Olivera, & Suzuki, 2008). Crosslinking of the high-affinity IgE receptor FcεRI on mast cells with IgE and antigen initiates signals leading to the release of allergic mediators such as histamine and eicosanoids that induce allergic inflammation. Activated mast cells produce PGD_2, LTB_4, and LTC_4 as main eicosanoids, and accumulating evidence suggests that mast cell-derived LTB_4 and LTC_4 exacerbate, while PGD_2 ameliorates, allergic diseases (Kanaoka, Maekawa, Penrose, Austen, & Lam, 2001; Nakamura et al., 2015; Ott, Cambier, Kappler, Marrack, & Swanson, 2003; Taketomi et al., 2013). The initiation of AA metabolism in mast cells depends solely on $cPLA_2\alpha$, an AA-selective intracellular PLA_2 which, upon FcεRI signaling, is activated by mitogen-activated protein kinases and undergoes Ca^{2+}-dependent translocation from the cytosol to perinuclear membranes, where downstream eicosanoid-biosynthetic enzymes reside (Clark et al., 1991; Lin et al., 1993; Ueno et al., 2011). Allergic responses, such as asthma, are attenuated in mice lacking $cPLA_2\alpha$ ($Pla2g4a^{-/-}$) or those treated with a $cPLA_2\alpha$ inhibitor (Malaviya et al., 2006; Uozumi et al., 1997). However, the roles of $sPLA_2$s in allergy in the context of mast cell biology in vivo have remained elusive over the last few decades.

Bee venom group III PLA_2, when injected into mouse skin, activates mast cells by hydrolysis of membrane phospholipids to release lysophosphatidylcholine (LPC), which causes cell lysis leading to activation of group 2 innate lymphoid cells by releasing the Th2-promoting cytokine IL-33 (Palm et al., 2013). Exogenous human PLA2G3 also facilitates mast

cell activation in mouse skin (Taketomi et al., 2013), and endogenous PLA2G3 is stored in and released from mouse mast cell granules. Importantly, mast cell-dependent passive and active anaphylactic responses are markedly attenuated in *Pla2g3*$^{-/-}$ mice and conversely augmented in *PLA2G3*-TG mice (Taketomi et al., 2013). This phenotype is mast cell autonomous, as bone marrow-derived mast cells from *Pla2g3*$^{-/-}$ mice fail to reconstitute the anaphylactic response after transfer to mast cell-deficient *Kit*$^{W\text{-}sh/W\text{-}sh}$ mice. Notably, mast cells in *Pla2g3*$^{-/-}$ mice are numerically normal but morphologically and functionally immature, indicating that PLA2G3 does not merely act as a mast cell activator but also facilitates mast cell maturation. Moreover, mast cell abnormalities observed in *Pla2g3*$^{-/-}$ mice are recapitulated in mice lacking lipocalin-type PGD_2 synthase (L-PGDS), which is expressed in neighboring fibroblasts, or those lacking the PGD_2 receptor DP1, which is induced in maturing mast cells. Pharmacological or genetic ablation of DP1 in mast cells or L-PGDS in fibroblasts phenocopies that of PLA2G3 in mast cells in terms of perturbed mast cell maturation and anaphylaxis (Taketomi et al., 2013).

Thus, PLA2G3 secreted from mast cells is coupled with fibroblastic L-PGDS to produce microenvironmental PGD_2, which then acts on DP1 on mast cells to promote their proper maturation (Fig. 6), an event that is also applicable to human mast cells. None of the other $sPLA_2s$ tested so far affects anaphylaxis, highlighting the specific role of PLA2G3 as an "anaphylactic $sPLA_2$." The PLA2G3/L-PGDS/DP1 paracrine circuit highlights a new aspect of PGD_2-DP1 signaling in the regulation of mast cell maturation and thereby allergy, and provides solid in vivo evidence that $sPLA_2$ acts as a paracrine coordinator of eicosanoid production in a tissue microenvironment (Starkl, Marichal, & Galli, 2013; Taketomi et al., 2013). A remaining question to be answered is whether mast cell-secreted PLA2G3 would target phospholipids in the plasma membrane of adjacent fibroblasts, microparticles shed from mast cells, or both.

6.2 Other Potential Functions

TG overexpression of PLA2G3 in *Apoe*$^{-/-}$ mice results in increased atherosclerosis due to accelerated lipoprotein hydrolysis and increased thromboxane synthesis (Sato et al., 2008). *PLA2G3*-TG mice also develop systemic inflammation as they age, probably due to increased eicosanoid generation (Sato et al., 2009). Furthermore, *PLA2G3*-transfected colon cancer cells have increased tumorigenicity when transplanted into nude mice

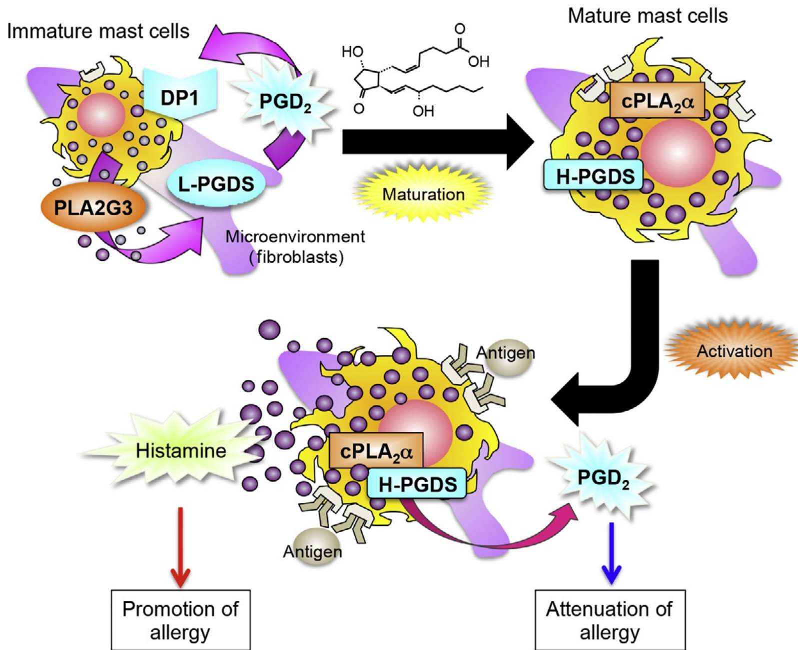
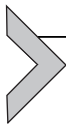


Fig. 6 Biological roles of PLA2G3 in mast cell maturation and anaphylaxis. PLA2G3 secreted from immature mast cells is coupled with fibroblastic L-PGDS to produce a microenvironmental pool of PGD_2, which acts on the PGD_2 receptor DP1 on immature mast cells to facilitate their functional maturation. Mature mast cells express higher levels of cPLA$_2$α and H-PGDS which, upon cross-linking of FcεRI by IgE and antigen, produce a distinct and large pool of PGD_2 that attenuates allergic responses.

(Murakami et al., 2005), and several lines of evidence suggest a positive correlation between PLA2G3 and human colon cancer (Hoeft et al., 2010; Kazama et al., 2015; Mounier et al., 2008). Thus, beyond the overexpression strategy, PLA2G3 appears to have proatherogenic, proinflammatory, and protumorigenic potential. Apart from immunological aspects, *Pla2g3*$^{-/-}$ mice display male infertility due to impairment of epididymal sperm motility and maturation (Sato et al., 2010). Mechanistically, PLA2G3 secreted from epididymal epithelial cells acts on spermatozoa passing through the epididymal duct to promote membrane phospholipid remodeling, which allows enrichment of docosapentaenoic acid (DPA) and DHA in sperm membrane phospholipids.

Recently, functional genomic screening has identified PLA2G3 as a negative regulator of ciliogenesis (Kim et al., 2010). Production of

lysophospholipids by PLA2G3, whose expression is upregulated by the transcription factor SREBP-1c, leads to distortion of endosomal recycling and vesicular trafficking for ciliogenesis (Gijs et al., 2015). The primary cilium is a microtubule-based organelle that projects from the surface of a wide variety of cells and acts as an antenna to sense extracellular cues and regulate diverse signaling pathways (Berbari, O'Connor, Haycraft, & Yoder, 2009; Christensen, Pedersen, Schneider, & Satir, 2007). Defects of cilium formation have been recognized as a central event in many types of pathologic states, including classical ciliopathies, obesity, and cancer (Fliegauf, Benzing, & Omran, 2007; Sen Gupta, Prodromou, & Chapple, 2009). Considering that PLA2G3 could affect inflammation, cancer, and sperm flagellar motility (see earlier), regulation of ciliogenesis might be a common mechanism underlying the functions of PLA2G3 in several pathophysiological events.



7. GROUP V $sPLA_2$ (PLA2G5)

PLA2G5 ($sPLA_2$-V) is often classified into the group II subfamily of $sPLA_2s$ since its gene is mapped to the group II $sPLA_2$ cluster locus, even though it does not possess some key features of group I and II $sPLA_2s$ (Chen, Engle, Seilhamer, & Tischfield, 1994a; Tischfield et al., 1996). PLA2G5 hydrolyzes PC more efficiently than PLA2G2A and other group II $sPLA_2s$ (Han et al., 1999), leading to the proposal that this $sPLA_2$ may participate in inflammation by driving AA metabolism from PC-rich mammalian cell membranes. However, it is now obvious that PLA2G5 releases fatty acids with a low degree of unsaturation, such as OA and LA, in favor of AA from cellular membranes, lipoproteins, and phospholipid vesicles (Chen & Dennis, 1998; Chen et al., 1994b; Mitsuishi et al., 2007; Murakami et al., 1998; Pruzanski et al., 2005). Therefore, PLA2G5 may drive some types of lipid metabolism in addition to, or even unrelated to, canonical AA metabolism to exert its biological actions in vivo. Indeed, the neonatal death of *PLA2G5*-TG mice arises from the ability of this enzyme to hydrolyze lung surfactant PC with saturated or monounsaturated fatty acids (ie, palmitic acid or palmitoleic acid), independently of eicosanoid generation (Ohtsuki et al., 2006). As described later, recent elegant studies have revealed unique features of PLA2G5 as a modulator of Th2 immunity ("Th2/M2-prone $sPLA_2$") and metabolic disorders ("metabolic $sPLA_2$") among others (Fig. 7).

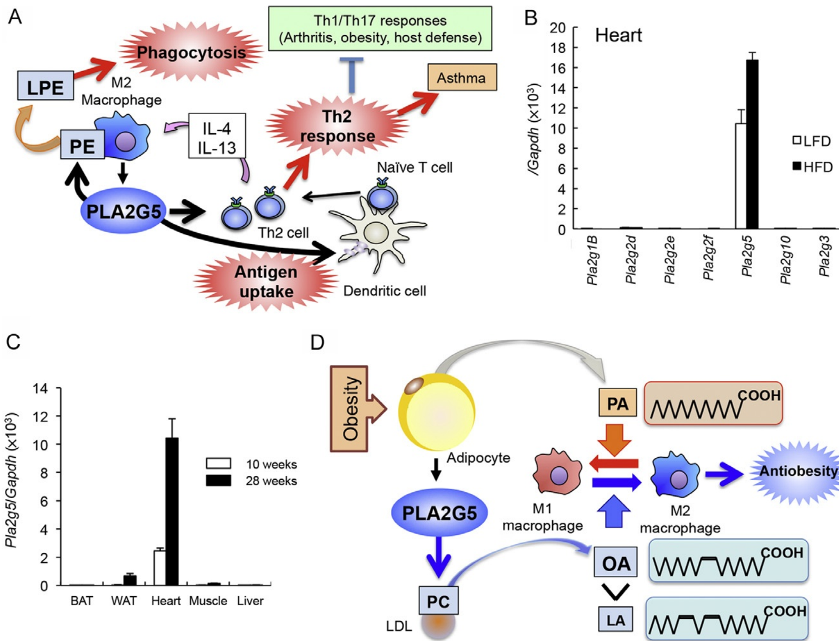


Fig. 7 Biological roles of PLA2G5 in Th2 immunity and metabolic syndrome. (A) The roles of PLA2G5 in Th2 immunity and phagocytosis. PLA2G5 is preferentially expressed in M2 macrophages and promotes phagocytosis and antigen uptake by macrophages and dendritic cells, possibly through production of LPE. PLA2G5 also facilitates Th2 skewing of antigen-presented T cells, although the mechanism that accounts for this Th2-promoting function remains unclear. Th2 immunity is associated with asthma, whereas it counteracts Th1/Th17-based immune responses. (B) PLA2G5 is a predominant sPLA$_2$ isozyme expressed in the heart of female mice after feeding a low-fat diet (LFD) or a high-fat diet (HFD) for 20 weeks. (C) Expression of *Pla2g5* in metabolically active tissues of female mice at 10 and 28 weeks under a LFD. Note that *Pla2g5* expression in the WAT as well as the heart is highly induced after HFD feeding (see text). (D) The metabolic role of PLA2G5. PLA2G5 is induced in adipocytes during obesity and hydrolyzes PC in LDL to release oleate and linoleate, which counteract palmitate-induced adipose tissue inflammation and thereby obesity-associated metabolic disorders. *PA*, palmitic acid.

7.1 Macrophage Phagocytosis

In line with the classical idea noted earlier, initial studies using *Pla2g5*$^{-/-}$ mice showed that PLA2G5 modestly augments zymosan-induced peritonitis or LPS-induced air pouch inflammation (Lapointe et al., 2010; Satake et al., 2004). However, subsequent studies, pioneered by Arm and coworkers, have shown that in several situations PLA2G5 exerts antiinflammatory

functions, which may rely on a common mechanism involving the regulation of macrophage phagocytosis by this $sPLA_2$. Peritoneal macrophages from *Pla2g5*$^{-/-}$ mice show reduced phagocytosis of fungi (yeast and *Candida albicans*) ex vivo, and *Pla2g5*$^{-/-}$ mice display severe systemic candidiasis with higher mortality due to an increased fungal burden in multiple tissues in vivo (Balestrieri et al., 2006, 2009). In this regard, PLA2G5 contributes to antifungal innate immunity by facilitating phagocytotic killing. Likewise, increased airway inflammation in *Pla2g5*$^{-/-}$ mice after *Escherichia coli* infection could be explained, in part, by reduced clearance of the bacterium by alveolar macrophages (Degousee et al., 2011). Arthritis is also exacerbated in *Pla2g5*$^{-/-}$ mice, where opsonization-driven clearance of the pathogenic immune complex by macrophages is hampered (Boilard et al., 2010). Exogenous supplementation or adenoviral transfer of PLA2G5 into *Pla2g5*$^{-/-}$ mice can rescue *Candida* clearance and ameliorate arthritis by facilitating macrophage phagocytosis of the fungi and immune complex, respectively. Conceivably, the opposing functions of PLA2G5 and PLA2G2A in protection from and promotion of arthritis, respectively, could explain why a pan-$sPLA_2$ inhibitor failed to exert a therapeutic effect on rheumatoid arthritis in a clinical study (Bradley et al., 2005).

As a potential mechanism for the regulation of phagocytosis, PLA2G5 may produce fusogenic lysophospholipids in membrane microdomains where fusion occurs between the plasma membrane and phagosome membrane. In line with this idea, it has recently been shown that PLA2G5 may facilitate phagocytosis of human macrophages through production of LPE (Rubio et al., 2015). Alternatively, PLA2G5 may affect the polarization of macrophages, thereby influencing their phacocytotic capacity (see later).

7.2 Th2 Immunity

Expression of PLA2G5 in the lung is elevated in patients with asthma or in mice subjected to asthma models, where it is localized to bronchial epithelial cells and alveolar macrophages (Munoz et al., 2007). *Pla2g5*$^{-/-}$ mice are protected from antigen-induced asthma and LPS- or ventilator-induced alveolar injury (Giannattasio et al., 2010; Henderson et al., 2013; Meliton et al., 2013; Munoz et al., 2007; Munoz, Meliton, Meliton, Dudek, & Leff, 2009; Ohta, Imamura, Xing, Boyce, & Balestrieri, 2013), indicating that PLA2G5 acts as a proinflammatory enzyme in the airway. Bone marrow transfer experiments have revealed that PLA2G5 in antigen-presenting cells

promotes antigen uptake and thereby antigen presentation to T cells for eliciting a Th2 response, while PLA2G5 in airway epithelial cells augments lung injury, probably through surfactant degradation (Giannattasio et al., 2010; Henderson et al., 2013; Ohta et al., 2013; Ohtsuki et al., 2006). Importantly, PLA2G5 is the only $sPLA_2$ isoform induced by the Th2 cytokines IL-4 and IL-13 in M2 macrophages and Th2 cells and promotes the Th2 immune response by facilitating IL-4 expression and IgE production by LN cells (Ohta et al., 2013; Rubio et al., 2015; Sato et al., 2014). Indeed, PLA2G5 expression in IL-4-driven M2 macrophages is sufficient for development of asthma induced by house dust mites (Ohta et al., 2013). The property of PLA2G5 as a "Th2/M2-prone $sPLA_2$" appears to fit with the view that *Pla2g5*$^{-/-}$ mice are protected from asthma (Th2 dependent; Giannattasio et al., 2010; Munoz et al., 2007), whereas they suffer from more severe infection (Th1 dependent) and arthritis (Th17 dependent) (Balestrieri et al., 2009; Boilard et al., 2010), where Th1/Th17 immunity is counterbalanced by Th2 immunity. This immune balance regulation by PLA2G5 toward a Th2/M2-prone state could thus explain why this enzyme exhibits pro- or antiinflammatory actions depending on distinct disease contexts. This notion may also be true for the metabolic role of PLA2G5, as described later. The roles of PLA2G5 in phagocytosis and Th2 immunity are illustrated in Fig. 7A.

7.3 Metabolic Diseases

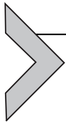
The incidence of metabolic syndrome has been increasing at an explosive rate worldwide due to a pandemic of obesity and type 2 diabetes resulting from overeating of high-caloric foods (Despres & Lemieux, 2006). The mechanisms connecting insulin resistance to obesity include an elevation of circulating lipids, ectopic lipid deposition leading to lipotoxicity, and chronic inflammation in metabolically active tissues (Hotamisligil, 2006). Among the $sPLA_2$s, PLA2G5 is highly induced in hypertrophic adipocytes of obese mice (Sato et al., 2014). This fact, along with the constitutive expression of PLA2G5 at relatively high levels in the heart, which has a high demand for lipids as an energy source (Fig. 7B), suggests that regulation of energy metabolism may be one of the primary roles of this $sPLA_2$. The levels of *Pla2g5* expression in WAT and the heart are markedly elevated in aged mice relative to young mice (Fig. 7C), perhaps reflecting its upregulation in age-related obesity and/or through an unknown mechanism.

On a high-fat diet (HFD), *Pla2g5*$^{-/-}$ mice display more severe metabolic disorders with increased obesity and hepatic steatosis, elevated levels of plasma low-density lipoprotein (LDL) levels, and exacerbated insulin resistance (Sato et al., 2014). Mechanistically, PLA2G5 protects against metabolic disorders by normalizing the lipid content in fat-overladen LDL and by tipping the immune balance toward an M2/Th2 state that counterregulates adipose tissue inflammation. Unsaturated fatty acids (OA and LA) released from PC in hyperlipidemic LDL by adipocyte-driven PLA2G5 prevent M1 polarization of adipose tissue macrophages by palmitic acid, a saturated fatty acid that promotes metabolic inflammation. Moreover, in agreement with the role of PLA2G5 in macrophage phagocytosis (see earlier), which might be a result of the altered M1/M2 macrophage ratio, HFD-fed *Pla2g5*$^{-/-}$ mice show impaired clearance of dead cells in adipose tissue. Overall, PLA2G5 allows adipose tissue to be in an antiinflammatory state by regulating the balance between detrimental saturated fatty acids and beneficial unsaturated fatty acids. Additionally, given that Th2 immunity counteracts metabolic diseases (Odegaard & Chawla, 2013), the reduced whole-body Th2/M2 status in *Pla2g5*$^{-/-}$ mice (see earlier) may also underlie the exacerbated metabolic outcomes. These results reveal the physiological importance of lipoprotein hydrolysis by sPLA$_2$ and highlight PLA2G5, a "metabolic sPLA$_2$," as an integrated regulator of metabolism and inflammation (Sato et al., 2014). The metabolic regulation by PLA2G5 is illustrated in Fig. 7D. Of note, *PLA2G5* expression in human adipose tissue inversely correlates with plasma LDL levels (Sato et al., 2014) and *PLA2G5* mutations are associated with LDL levels in patients with type 2 diabetes or obesity (Sergouniotis et al., 2011; Wootton et al., 2007), implying the relevance of these findings to humans.

7.4 Cardiovascular Diseases

Prior to discovery of the role of PLA2G5 as a "metabolic sPLA$_2$" as described earlier, this enzyme has long been implicated in atherosclerosis. In this scenario, sPLA$_2$-mediated hydrolysis of LDL gives rise to a type of proatherogenic small-dense LDL with an increased net negative charge, LPC content, and aggregation propensity (Hanasaki et al., 2002; Wooton-Kee, Boyanovsky, Nasser, de Villiers, & Webb, 2004). Treatment of LDL with several sPLA$_2$s (X > V > III > IIF > IIA in rank order) facilitates the hydrolysis of phospholipids and thereby the formation of lipid-laden

foam cells from macrophages in vitro (Boyanovsky, van der Westhuyzen, & Webb, 2005; Hanasaki et al., 2002; Sato et al., 2008), a hallmark feature of atherosclerosis. However, the in vivo relevance of this phenomenon remains controversial. *Ldlr*$^{-/-}$ mice transferred with *Pla2g5*$^{-/-}$ bone marrow cells are modestly protected from atherosclerosis (Bostrom et al., 2007), whereas global *Pla2g5* deficiency on an *Apoe*$^{-/-}$ background does not affect plaque formation (Boyanovsky, Zack, Forrest, & Webb, 2009). Although the former study suggested that hematopoietic (probably macrophage) PLA2G5 contributes partially to atherosclerosis development, plasma LDL levels are unaffected by *Pla2g5* ablation in both cases, arguing against the proposed role of PLA2G5 in LDL metabolism under atherosclerotic conditions. Contradictory results have also been reported for the roles of PLA2G5 in cardiac disorders, where *Pla2g5* ablation aggravates cardiac fibrosis (Boyanovsky, Bailey, Dixon, Shridas, & Webb, 2012), whereas conversely it attenuates myocardial infarction and aneurysm (Boyanovsky et al., 2012; Yano et al., 2011). Moreover, a pan-sPLA$_2$ inhibitor failed to show efficacy in a phase III clinical trial in the context of cardiovascular disease (Nicholls et al., 2014). Thus, PLA2G5 or any other conventional sPLA$_2$s may not contribute significantly to atherosclerosis or related cardiovascular disorders, even though it may promote or suppress them under certain conditions. Rather, LDL hydrolysis by PLA2G5 appears to be relevant to obesity-related metabolic syndrome, as described earlier.



8. GROUP X sPLA$_2$ (PLA2G10)

PLA2G10 (sPLA$_2$-X) has both group I- and group II-like structural features, suggesting that it emerged during diversification from group I to II sPLA$_2$s (Cupillard et al., 1997). As in the case of PLA2G1B (see later), PLA2G10 is synthesized as a zymogen, and removal of an N-terminal propeptide produces an active mature enzyme. This processing may occur extracellularly after secretion, as is the case for many digestive enzymes in the GI tract, or intracellularly before secretion by furin-like convertases (Jemel et al., 2011; Layne, Shridas, & Webb, 2015; Masuda et al., 2005). Among the sPLA$_2$s, PLA2G10 has the highest affinity for PC and thus exhibits the most potent ability to hydrolyze plasma membrane phospholipids in intact cells (Bezzine et al., 2000; Murakami et al., 2001). Because of this property, many studies have been performed under the assumption that PLA2G10 plays a proinflammatory role by mobilizing AA metabolism.

This notion may indeed be correct in some situations, but here we draw attention to several important aspects of this enzyme, which appear to have been forgotten or ignored by many investigators.

First, the tissue distribution of PLA2G10 is not ubiquitous, being expressed almost exclusively in the GI tract and testis and to a much lesser extent in the lung (Fig. 2) (Sato et al., 2011). At least in mice, expression of PLA2G10, relative to several other $sPLA_2s$, is fairly low or undetectable in most immune cells. Of course, this does not exclude the possibility that PLA2G10 is expressed in some immune cell populations under certain conditions, but the notion that the enzyme is expressed widely in immune cells, where it plays immunoregulatory roles, is apparently misleading and needs to be reassessed carefully. Second, as PLA2G10 is a very powerful $sPLA_2$ for hydrolysis of cellular membranes, it is capable of releasing AA from any cell types, even cells that do not intrinsically express PLA2G10 at all, when supplied artificially. Hence, even if PLA2G10-transfected cells were capable of releasing AA robustly, this would not necessarily reflect its physiological function. Third, PLA2G10 shows an apparent PUFA preference, releasing ω3 PUFAs such as EPA, DPA, and DHA in addition to, or even preferentially to, ω6 AA from cultured cells, lipoproteins, or even tissues (Murase et al., 2016). However, the ability of PLA2G10 to release ω3 PUFAs in vivo and the resulting pathophysiological outcomes has not been taken into consideration. Here, we focus mainly on the established roles of PLA2G10 in specific tissues where this enzyme is endogenously expressed at substantial levels and drives ω6 or ω3 lipid metabolism.

8.1 Asthma and Airway Inflammation

Several studies have demonstrated that PLA2G10 is expressed in pulmonary epithelial cells, although at much lower levels than in the GI tract and testis. Perhaps asthma is the best-studied disease in which PLA2G10 exerts proinflammatory functions through AA metabolism. *Pla2g10*$^{-/-}$ mice show resistance to antigen-induced asthma, with marked reductions of eosinophil infiltration, goblet cell hyperplasia, smooth muscle layer thickening, and pulmonary eicosanoid synthesis (Henderson et al., 2007). The attenuated asthmatic responses in *Pla2g10*$^{-/-}$ mice are restored by knock-in of the human *PLA2G10* gene, and treatment of these knock-in mice with an inhibitor specific for human PLA2G10 attenuates pulmonary inflammation (Henderson et al., 2011). Unlike

PLA2G5 (see earlier), however, PLA2G10 does not influence the Th2 response itself, since IgE and IL-4 levels are unaffected in *Pla2g10*$^{-/-}$ mice (Henderson et al., 2013). Mechanistically, PLA2G10 secreted from the airway epithelium may act on infiltrating eosinophils in a paracrine manner to trigger the LPC-dependent activation of cPLA$_2$α for LTC$_4$ biosynthesis (Hallstrand et al., 2016; Lai et al., 2010). Selective inhibition of PLA2G10 attenuates the fMLP-induced release of AA and LTC$_4$ by human eosinophils, suggesting an autocrine amplification of AA metabolism through the coordinated action of eosinophil-secreted PLA2G10 and intracellular cPLA$_2$α (Hallstrand et al., 2016). In addition, PLA2G10 is induced during in vitro differentiation of airway epithelial cells, from which it appears to elicit AA release directly (Hallstrand et al., 2013). *Pla2g10*$^{-/-}$ mice are also partially protected from the early phase of lung inflammation following influenza infection (Kelvin et al., 2014). Moreover, PLA2G10 is a major sPLA$_2$ isoform detected in the airway of patients with asthma (Hallstrand et al., 2011). Thus, PLA2G10, an "asthmatic sPLA$_2$," may be a novel therapeutic target for asthma or other inflammatory diseases in the airway.

8.2 Colitis

Contrary to the proposal that PLA2G10 promotes inflammation, *PLA2G10*-TG mice display striking immunosuppressive and lean phenotypes with lymphopenia and increased M2-like macrophages (Murase et al., 2016). This phenotype is accompanied by marked elevation of antiinflammatory ω3 PUFAs and their metabolites in multiple tissues, indicating for the first time that PLA2G10 has the capacity to release ω3 PUFAs in vivo. In an effort to obtain physiological insight into this phenomenon, studies using *Pla2g10*$^{-/-}$ mice have demonstrated that endogenous PLA2G10, which is expressed abundantly in the colon epithelium as a "gastrointestinal sPLA$_2$," mobilizes ω3 PUFAs and their metabolites, rather than ω6 AA metabolites, thereby protecting the tissue from dextran sulfate (DSS)-induced colitis (Murase et al., 2016). *Pla2g10* deficiency increases the colorectal expression of Th17 cytokines, and ω3 PUFAs themselves attenuate the production of these cytokines by lamina propria cells from DSS-treated mice, at least in part through the PUFA receptor GPR120. In comparison, the production of colon-protective prostanoids, such as PGE$_2$ (Kabashima et al., 2002), is regulated mainly by cPLA$_2$α

(Murase et al., 2016). These results underscore a previously unappreciated role of PLA2G10 as an ω3 PUFA mobilizer in vivo, segregated mobilization of ω3 and ω6 PUFAs by PLA2G10 and $cPLA_2\alpha$, respectively, in protection against colitis, and a functional connection between a particular $sPLA_2$ and a PUFA-sensing receptor (Fig. 8A and B).

8.3 Cardiovascular Diseases, Metabolic Syndrome, and Beyond

Herein, we overview several phenotypes of *Pla2g10*$^{-/-}$ mice in the contexts of cardiovascular and metabolic diseases, although conflicting results have been reported. *Pla2g10*$^{-/-}$ mice are protected from myocardial infarction or aneurysm (Fujioka et al., 2008; Watanabe et al., 2012; Zack et al., 2011). Different groups have reported opposite (promoting or protecting) atherosclerotic phenotypes in *Pla2g10*$^{-/-}$ mice (Ait-Oufella et al., 2013; Zack et al., 2011). In humans, it has been reported that *PLA2G10* gene polymorphisms are negatively correlated with a risk of recurrent cardiovascular events or not associated with such a risk (Gora et al., 2009; Guardiola et al., 2015). *Pla2g10*$^{-/-}$ mice display increased or reduced adiposity (Li, Shridas, Forrest, Bailey, & Webb, 2010; Sato et al., 2011), altered or unaltered macrophage functions (Shridas et al., 2011), increased adrenal steroidogenesis probably through PUFA-mediated perturbation of nuclear receptor signaling (Shridas et al., 2010), or altered insulin secretion by pancreatic β cells, perhaps due to reduced PGE_2 synthesis (Shridas, Zahoor, Forrest, Layne, & Webb, 2014). As PLA2G10 is expressed abundantly in the gut epithelium, decreased digestion of dietary and biliary phospholipids may be eventually associated with the reduced adiposity in *Pla2g10*$^{-/-}$ mice (Sato et al., 2011), a situation similar to that in *Pla2g1b*$^{-/-}$ mice (see later). Alternatively, PLA2G10 in the GI tract might alter the microbiota, which could secondarily affect both immune and metabolic balance (Ley et al., 2005; Mazmanian, Liu, Tzianabos, & Kasper, 2005; Tremaroli & Backhed, 2012). This could explain some of the discrepancies observed in *Pla2g10*$^{-/-}$ mice maintained in different facilities, although this will require experimental confirmation.

Apart from immunologic considerations, preference of PLA2G10 for ω3 PUFAs is also observed in spermatozoa, another site where this $sPLA_2$ is highly expressed. There, PLA2G10 secreted from sperm acrosomes acts on sperm membranes to mobilize ω3 DPA and DHA, the former promoting the ability of spermatozoa to fertilize oocytes (Escoffier et al., 2010; Murase et al., 2016; Sato et al., 2011).

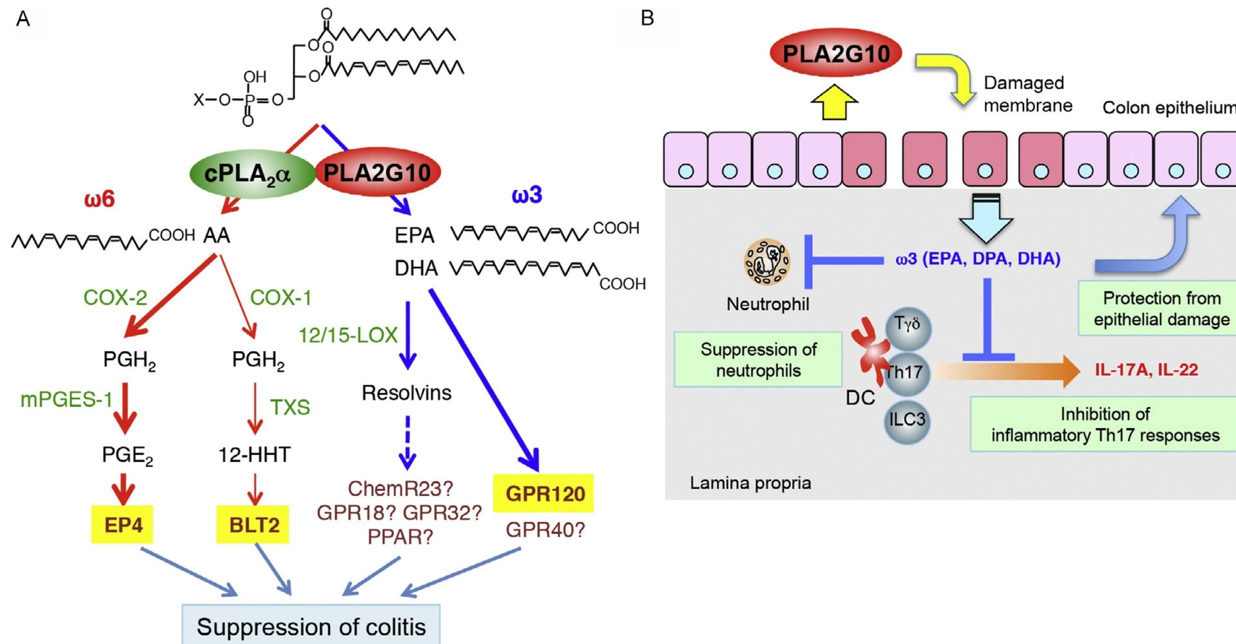
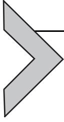


Fig. 8 Biological roles of PLA2G10 in protection against colitis. (A) In DSS-induced colitis, both cPLA$_2$α and PLA2G10 suppress intestinal inflammation, where cPLA$_2$α is coupled with the AA-derived PGE$_2$-EP4 and 12-HHT-BLT2 axis, while PLA2G10 is coupled with the ω3 PUFA-GPR120 axis. *COX*, cyclooxygenase; *LOX*, lipoxygenase; *mPGES*, microsomal PGE$_2$ synthase; *TXS*, thromboxane synthase; *EP4*, PGE$_2$ receptor 4; *12-HHT*, 12-hydroxyheptadecatrenoic acid; *BLT2*, the second LTB$_4$ receptor. (B) A schematic model for the role of PLA2G10 in protection against colitis. PLA2G10 preferentially releases ω3 PUFAs from (damaged) epithelial cells. These ω3 PUFAs, by themselves or after being metabolized to resolvins, prevent proinflammatory Th17-type immune responses and probably act directly on epithelial cells to protect them from injury, and on neutrophils to suppress their migration and promote their clearance.



9. OTHER sPLA$_2$s AND sPLA$_2$ RECEPTOR (PLA2R1)

Here, we overview other sPLA$_2$s, whose roles in immunity in vivo are not well understood. We also briefly describe PLA2R1, an integral membrane protein that binds to conventional sPLA$_2$s.

9.1 Other sPLA$_2$s

PLA2G1B (sPLA$_2$-IB), a prototypic isoform often referred to as pancreatic sPLA$_2$, is secreted from pancreatic acinar cells into the intestinal lumen, where an N-terminal heptapeptide of the zymogen is cleaved by trypsin to yield an active enzyme (Seilhamer, Randall, Yamanaka, & Johnson, 1986; Verheij, Westerman, Sternby, & De Haas, 1983). Although the immunological function of PLA2G1B is unknown, *Pla2g1b*$^{-/-}$ mice are refractory to diet-induced metabolic disorders and atherosclerosis (Hollie & Hui, 2011; Hollie, Konaniah, Goodin, & Hui, 2014; Huggins, Boileau, & Hui, 2002; Labonte et al., 2006), suggesting that absence of PLA2G1B may indirectly ameliorate metabolic inflammation. These phenotypes in *Pla2g1b*$^{-/-}$ mice are most likely explained by reduced digestion of dietary and biliary phospholipids in the GI tract (Huggins et al., 2002). Accordingly, the reduced production and absorption of LPC in the GI tract, a causal factor for insulin resistance, leads to protection from metabolic disorders (Hollie & Hui, 2011; Hollie et al., 2014; Labonte et al., 2006). On the other hand, pancreatic acinar cell-specific *Pla2g1b*-TG mice develop more severe obesity and insulin intolerance (Cash et al., 2011). Oral administration of a cell-impermeable pan-sPLA$_2$ inhibitor to mice attenuates diet-induced obesity and diabetes by inhibiting PLA2G1B (and probably PLA2G10) in the GI tract (Hui et al., 2009). Thus, pharmacological inhibition of PLA2G1B, a "digestive sPLA$_2$," could be an effective oral therapy for metabolic diseases.

PLA2G2C (sPLA$_2$-IIC) is a member of the group II sPLA$_2$s with a unique extra sequence in the middle region of the molecule and is expressed abundantly in rodent testis (Chen et al., 1997). However, since this sPLA$_2$ is a pseudogene and not expressed as a functional protein in humans (Tischfield et al., 1996), no analysis of *Pla2g2c*$^{-/-}$ mice has been conducted. Nonetheless, in relation to immunity, a *Pla2g2c* knockdown study has demonstrated that PLA2G2C is induced in mouse hepatocytes after infection with hepatitis B to produce LPE, a lysophospholipid antigen. LPE is then presented to

CD1d on NKT cells, leading to propagation of an antivirus immune response (Zeissig et al., 2012). It remains unknown whether other $sPLA_2$s may compensate for this function of PLA2G2C in human hepatocytes.

PLA2G2E ($sPLA_2$-IIE), like PLA2G2D, is structurally most homologous to PLA2G2A (Valentin, Ghomashchi, et al., 1999). PLA2G2E is another "metabolic $sPLA_2$" that is markedly induced in adipocytes of obese mice. *Pla2g2e*$^{-/-}$ mice are modestly protected from diet-induced obesity, fatty liver, and hyperlipidemia, without any accompanying alteration of adipose tissue inflammation (Sato et al., 2014). Mechanistically, PLA2G2E hydrolyzes the minor lipoprotein phospholipids, PE and PS, thereby affecting lipoprotein-mediated lipid delivery to adipose tissue and liver. Unlike the situation in mice, however, PLA2G2A rather than PLA2G2E is highly expressed in human or rat adipose tissue, where PLA2G2A might act in place of PLA2G2E. Indeed, administration of a PLA2G2A-specific inhibitor to rats prevents metabolic disorders (Iyer et al., 2012). In humans, a polymorphism in the *PLA2G2E* gene is associated with ulcerative colitis (Yang et al., 2013).

Lastly, PLA2G12A and PLA2G12B ($sPLA_2$-XIIA and -XIIB, respectively) belong to the atypical group XII $sPLA_2$ subfamily that has very unique structural and functional features (Gelb, Valentin, Ghomashchi, Lazdunski, & Lambeau, 2000; Rouault, Bollinger, Lazdunski, Gelb, & Lambeau, 2003). So far, there have been no reports of the immunological roles of these $sPLA_2$s in vivo. Interestingly, PLA2G12A kills Gram-negative bacteria such as *Helicobacter pylori* even more efficiently than PLA2G2A in vitro (Huhtinen et al., 2006; Koduri et al., 2002), suggesting its potential role in host defense. Deficiency of PLA2G12B, a catalytically inactive isoform in which the active center His is replaced by Leu (Rouault et al., 2003), leads to reduced secretion of very-low-density lipoprotein from the liver (Guan, Qu, Tan, Chen, & Wong, 2011), although the mechanism underlying this phenotype is entirely unclear.

9.2 PLA2R1

PLA2R1, also known as Clec13c belonging to the C-type lectin family, binds to several conventional $sPLA_2$s with distinct affinities in a species-specific manner (Rouault et al., 2007). PLA2R1 may act as a clearance receptor that inactivates $sPLA_2$s, as a signaling receptor that transduces $sPLA_2$-dependent signals in a catalytic activity-independent manner, or as

a pleiotropic receptor that binds to non-$sPLA_2$ ligands (Valentin & Lambeau, 2000). In allergen-induced asthma, the lungs of *Pla2r1*$^{-/-}$ mice display advanced inflammation, accompanied by greater accumulation of PLA2G1B and PLA2G10 proteins (Tamaru et al., 2013), providing the first in vivo evidence that PLA2R1 serves as a clearance receptor for these $sPLA_2s$. In myocardial infarction, *Pla2r1*$^{-/-}$ mice exhibit higher rates of cardiac rupture and myofibroblast activation (Mishina et al., 2014), where PLA2R1, by interacting with integrin, may transmit $sPLA_2$-dependent signals to augment myofibroblast-driven wound healing or may facilitate the clearance of offensive $sPLA_2s$ (eg, PLA2G5 or PLA2G10). *Pla2r1*$^{-/-}$ mice have higher susceptibility to skin tumorigenesis (Vindrieux et al., 2013), which may be based on the $sPLA_2$-independent function of PLA2R1 in senescence or on the impaired clearance of skin-resident offensive $sPLA_2s$ (eg, PLA2G2F). Finally, PLA2R1 is a major autoantigen in membranous nephropathy, a severe autoimmune disease leading to podocyte injury and proteinuria (Beck et al., 2009; Stanescu et al., 2011). However, it is not clear whether the role of PLA2R1, which is expressed in podocytes, is $sPLA_2$ dependent or independent, or whether $sPLA_2s$ play some roles in the glomerulus by being supplied from the circulation or from mesangial cells, which are known to secrete PLA2G2A under inflammatory conditions (Beck et al., 2003).

10. PERSPECTIVES

Studies during the last decade have uncovered the pathophysiological functions of nearly a full set of $sPLA_2s$. Individual $sPLA_2s$ play unique and tissue-specific roles by driving canonical AA metabolism or noncanonical lipid pathways in immunology, metabolism, cancer, or other biological events by hydrolyzing different phospholipid components in various extracellular milieus. Nonetheless, since most of our present knowledge on the functions of $sPLA_2s$ has been based on the results of studies using knockout and/or transgenic mice, it is important to translate these findings to humans. Association of $sPLA_2s$ with human diseases and their relationships with phenotypes seen in $sPLA_2$ gene-manipulated mice are summarized in Table 1. Hopefully, during the next decade, we will gain a more comprehensive picture of the $sPLA_2$-driven lipid networks, thus allowing the therapeutic application of inhibitors for some $sPLA_2s$ or $sPLA_2$-driven lipid products to human diseases.

Table 1 Possible Linkages Between sPLA$_2$s and Diseases in Humans and Relevant Phenotypes in sPLA$_2$ Knockout/Transgenic Mice

Human sPLA$_2$s	Human Diseases Associated with sPLA$_2$s	References	Mouse sPLA$_2$s	Related Phenotypes (KO)	Related Phenotypes (TG)	References
PLA2G1B	Obesity	Wilson et al. (2006)	*Pla2g1b*	Decreased obesity		Labonte et al. (2006)
					Increased obesity	Cash et al. (2011)
PLA2G2A	Gastric cancer	Leung et al. (2002)	*Pla2g2a*	Increased colon cancer		MacPhee et al. (1995)
					Decreased colon cancer	Cormier et al. (1997)
	Cardiovascular diseases	Kugiyama et al. (1999) Wootton et al. (2006)		N.D.	Increased atherosclerosis	Ivandic et al. (1999) Webb et al. (2003)
PLA2G2D	Chronic obstructive pulmonary disease	Takabatake et al. (2005)	*Pla2g2d*	Decreased viral-induced pneumonia	N.D.	Vijay et al. (2015)
PLA2G2E	Ulcerative colitis	Yang et al. (2013)	*Pla2g2e*	N.D.	N.D.	
PLA2G2F	Psoriasis	Yamamoto et al. (2015)	*Pla2g2f*	Decreased psoriasis	Increased psoriasis	Yamamoto et al. (2015)
PLA2G3	Colorectal cancer	Hoeft et al. (2010)	*Pla2g3*	N.D.	N.D.	
	Acquired immune deficiency syndrome	Limou et al. (2008)		N.D.	N.D.	
	Alzheimer's disease	Martínez-García et al. (2010)		N.D.	N.D.	
PLA2G5	Obesity and type 2 diabetes	Sato et al. (2014)	*Pla2g5*	Increased obesity and hyperlipidemia	N.D.	Sato et al. (2014)
	Retina degeneration	Wootton et al. (2007) Sergouniotis et al. (2011)		N.D.	N.D.	
PLA2G10	Decreased risk of atherosclerosis	Gora et al. (2009)	*Pla2g10*	Increased atherosclerosis	Decreased atherosclerosis	Ait-Oufella et al. (2013)

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