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Review

Selectivity of phospholipid hydrolysis by phospholipase A_2 enzymes in activated cells leading to polyunsaturated fatty acid mobilization☆

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ABSTRACT

Phospholipase A_2s are enzymes that hydrolyze the fatty acid at the *sn*-2 position of the glycerol backbone of membrane glycerophospholipids. Given the asymmetric distribution of fatty acids within phospholipids, where saturated fatty acids tend to be present at the *sn*-1 position, and polyunsaturated fatty acids such as those of the omega-3 and omega-6 series overwhelmingly localize in the *sn*-2 position, the phospholipase A_2 reaction is of utmost importance as a regulatory checkpoint for the mobilization of these fatty acids and the subsequent synthesis of proinflammatory omega-6-derived eicosanoids on one hand, and omega-3-derived specialized pro-resolving mediators on the other. The great variety of phospholipase A_2s, their differential substrate selectivity under a variety of pathophysiological conditions, as well as the different compartmentalization of each enzyme and accessibility to substrate, render this class of enzymes also key to membrane phospholipid remodeling reactions, and the generation of specific lipid mediators not related with canonical metabolites of omega-6 or omega-3 fatty acids. This review highlights novel findings regarding the selective hydrolysis of phospholipids by phospholipase A_2s and the influence this may have on the ability of these enzymes to generate distinct lipid mediators with essential functions in biological processes. This brings a new understanding of the cellular roles of these enzymes depending upon activation conditions.

1. Introduction

It is well established that the fatty acyl chains of membrane lipids play a wide variety of biological functions including signaling; thus the enzymes regulating phospholipid fatty acid recycling constitute a key step for the fine regulation of lipid mediator production during cell activation.

A prime example of bioactive fatty acid is arachidonic acid (20:4*n-6*, AA), an omega-6 fatty acid that is found at relatively high levels in cells involved in innate immunity reactions, such as monocytes, macrophages and dendritic cells [1–3]. AA is the common precursor of the eicosanoids, a family of lipid mediators with fundamental roles in physiology and pathophysiology, particularly in inflammatory reactions [4–6]. The eicosanoids affect immune regulation by modulating cell activation at different points, including differentiation and migration, phagocytic capacity, and cytokine production [7–10].

Similarly, docosahexaenoic acid (22:6*n-3*, DHA) and related long-chain omega-3 fatty acids eicosapentaenoic acid (20:5*n-3*, EPA) and docosapentaenoic acid (22:5*n-3*, DPA), also found in major inflammatory cells, can be oxygenated to generate biomolecules known as protectins, resolvins, and maresins (collectively called specialized pro-resolving mediators, SPM), which account for much of the biological activity of omega-3 fatty acids, and are involved in the resolution phase of inflammation, clearance of apoptotic cells, tissue repair and regeneration, and anti-nociceptive actions [11]. In addition, omega-3 fatty acids may promote anti-inflammatory reactions by themselves by acting on fatty acid-sensing receptors [12,13].

Fatty acid-derived mediators are produced during inflammation in two temporal waves with opposite effects, when cells switch the type of mediators produced from pro- to anti-inflammatory [14]. Thus, the

Abbreviations: AA, arachidonic acid; DHA, docosahexaenoic acid; DPA, docosapentaeonic acid; EPA, eicosapentaenoic acid; PLA_2, phospholipase A_2; $sPLA_2$, secreted phospholipase A_2; $iPLA_2$, calcium-independent phospholipase A_2; $cPLA_2$, cytosolic phospholipase A_2; CoA-IT, CoA-independent transacylase; PC, choline glycerophospholipid; PE, ethanolamine glycerophospholipid; PI, phosphatidylinositol; LPC, choline lysoglycerophospholipid; LPE, ethanolamine lysoglycerophospholipid; SPM, specialized pro-resolving mediators

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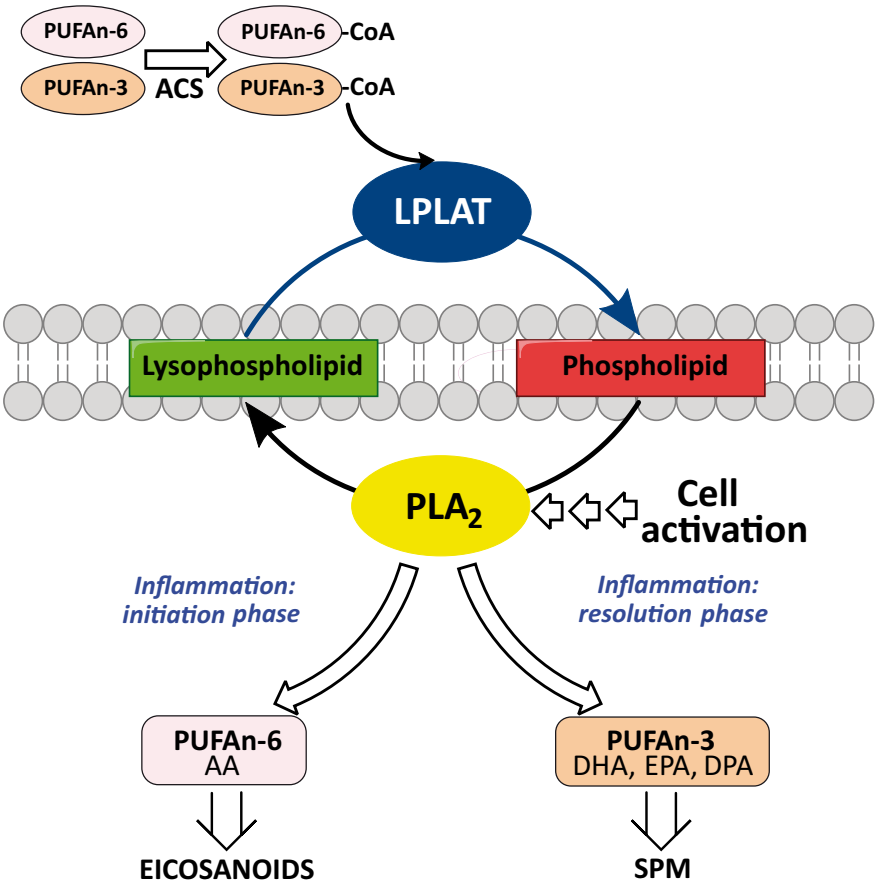

Fig. 1. Control of cellular fatty acid esterification to the *sn*-2 position of membrane phospholipids. This tightly controlled process involves the following events: PLA_2-mediated hydrolysis; activation of the free fatty acid by acyl-CoA synthetases (ACS); and re-incorporation into the *sn*-2 position of phospholipids by lysophospholipid:acyl-CoA acyltransferases (LPLAT). In stimulated cells the dominant reaction is the PLA_2-mediated deacylation step, which results in a dramatic increase in the levels of free fatty acid, which is now available for the synthesis of lipid mediators in the acute phase of inflammation (eicosanoids, derived from AA), and in the resolution phase of inflammation (pro-resolving lipid mediators derived from DHA, EPA or DPA).

immediate production of proinflammatory AA-derived eicosanoids after the insult is progressively followed by accumulation of anti-inflammatory lipoxins and other pro-resolving lipid mediators derived from omega-3 fatty acids, a process that initiates resolution of inflammation and the return to homeostasis [11,14]. Thus, cells appear to possess intrinsic mechanisms to dampen inflammation to avoid excessive damage that might lead to irreversible injury.

In addition to the expression of polyunsaturated fatty acid-metabolizing enzymes, availability of the fatty acid in free form is well established to constitute a limiting factor for the biosynthesis of eicosanoids and pro-resolving lipid mediators [1,15]. Such free fatty acid availability is provided by phospholipase A_2s, the enzymes that cleave the *sn*-2 position of glycerophospholipids [16]. Multiple PLA_2 enzymes co-exist in a single cell, each exhibiting potentially different headgroup and/or fatty acid preferences. Acting frequently in a co-ordinate manner, cellular PLA_2s provide a tight regulation of biological processes involving membrane phospholipid fatty acid rearrangement (Fig. 1). PLA_2s are found in practically all types of organisms, and in mammals they are ubiquitously expressed throughout most cells and tissues, suggesting their importance in life processes. The variety of functions of PLA_2s in physiology, far from being only circumscribed to activated states of immune cells, have become more evident in the last years with the study of the phenotypes of genetically-manipulated mice [16,17].

More than thirty enzymes with PLA_2 activity have been described and, based on sequence similarities, they are currently classified in 16 groups, each containing several sub-groups [16]. However, based on biochemical features these enzymes are frequently grouped into six major families: secreted phospholipase A_2s (sPLA$_2$), calcium-independent phospholipase A_2s (iPLA$_2$), cytosolic phospholipase A_2s (cPLA$_2$), platelet activating factor acetylhydrolases (PAF-AH, also known as lipoprotein-associated phospholipase A_2, Lp-PLA$_2$), lysosomal phospholipase A_2 (L-PLA$_2$) and the adipose phospholipase A (AdPLA$_2$) [16–20]. Extensive *in vitro* kinetic studies have been recently carried out with most of these enzymes. Many of the studies have taken advantage of the analytical power of mass spectrometry-based lipidomics [21–24], which provided valuable information as to the substrate preference of these enzymes. Nevertheless, factors that take part in the microenvironment of the enzymes, such as the complex membrane composition, compartmentalization of the enzyme and the different physiological and pathophysiological scenarios of the cell (including cross-talk between PLA_2 forms), may produce as a result a variety of lipid molecules that orchestrate global responses and cannot be easily reproduced in *in vitro* assays.

In general terms, PLA_2s participate in the Lands cycle of phospholipid fatty acid recycling [1,15,25], whereby the fatty acid composition at the *sn*-2 position of phospholipids is tightly controlled by a balance between hydrolytic reactions mediated by PLA_2s *versus* activation of the free fatty acid by acyl-CoA synthetases and subsequent incorporation into phospholipids by lysophospholipid:acyl-CoA acyltransferases. Further remodeling reactions also occur that are catalyzed primarily by CoA-independent transacylase (CoA-IT) [15,26,27]. In resting cells the reacylation reactions dominate, but in stimulated cells the dominant reaction is the PLA_2-mediated deacylation step, which results in a dramatic increase in the levels of free fatty acids, notably AA and omega-3 fatty acids, which will now be available for eicosanoid [1,14,15,28,29] or SPM [30–32] synthesis, depending on the temporal phase of the activation process (Fig. 1).

While our current knowledge on the mechanisms governing the expression levels of PLA_2s both at gene and protein level is still scarce for the majority of members of this superfamily of enzymes, much information has accumulated on the cellular regulation of their enzymatic activities and *in vitro* substrate preferences. This review is aimed at relating recent findings on the ability of PLA_2s to selectively hydrolyze

different phospholipid substrates in cells with the generation of bioactive lipid mediators. Key current studies are discussed, focusing primarily on cPLA$_2$α, iPLA$_2$-VIA, sPLA$_2$-V and sPLA$_2$-X, as these are the PLA$_2$ forms classically involved in the production of fatty acid-derived mediators [15,33–36].

2. Group IVA phospholipase A$_2$ (cPLA$_2$α)

Group IVA PLA$_2$, also known as cytosolic phospholipase A$_2$α (cPLA$_2$α), is long known to exhibit marked preference for phospholipid substrates containing AA at the *sn*-2 position. The aromatic residues of cPLA$_2$α interact with the double bonds of AA, making the enzyme selective for this fatty acid. cPLA$_2$α also displays significant activity towards EPA but, very remarkably, it shows little or no activity towards DHA [21,24,37]. This may be related to the fact that, unlike AA or EPA, DHA does not have a double bond at C5; thus the fatty acid does not adjust well within the cPLA$_2$α's active site [16,24,37,38].

cPLA$_2$α is widely accepted as the critical enzyme regulating AA mobilization in cells under a wide variety of activation conditions [39–42]. Various cross-talk mechanisms involving cPLA$_2$α and sPLA$_2$ have been described that result in amplified AA mobilization responses [43–50]. A number of recent reviews are available that cover in a comprehensive manner different aspects of cPLA$_2$α biochemistry and cell regulation, and the reader is kindly referred to these for specific details [15,16,33,51–53]. In the following we focus on recent studies that have unveiled previously unrecognized cellular roles and modes of regulation of cPLA$_2$α activity.

First of all, it should be emphasized that, although cPLA$_2$α manifests a marked selectivity for phospholipids that contain AA at the *sn*-2 position, this does not mean in any way that, in cells, the enzyme cannot hydrolyze other fatty acyl residues to a significant extent even if this occurs at a lower rate [24]. This points out the importance of cellular compartmentalization in the regulation of biological activity, *i.e.* the phospholipid fatty acid composition of the membrane to which the enzyme translocates during cell activation. In this regard, it has been recently shown that cPLA$_2$α is not only instrumental in effecting AA mobilization for eicosanoid production during inflammation reactions, but also regulates membrane phospholipid remodeling leading to the formation of phospholipid molecules with defined composition that participate in the execution of other responses such as generation of reactive oxygen species and secretion of bactericidal hydrolases [54]. One of such molecules is an unusual PI species which contains arachidonate at both the *sn*-1 and *sn*-2 positions of glycerol [55,56]. In addition to its biological roles in innate immune reactions mentioned above [54], this is a short-lived species that may also act as a transient acceptor for the incorporation of arachidonic acid into various cellular phospholipid classes [56]. Owing to its high arachidonic acid content, PI is also a major source for the release of this fatty acid *via* cPLA$_2$α in activated immune cells [55,57].

In vitro studies suggest that cPLA$_2$α does not show clear preference for the headgroup present at the *sn*-3 position, although a slight preference for zwitterionic phospholipids such as PC and PE has recently been pointed out [24]. In this regard, mass spectrometry analyses of glycerophospholipid hydrolysis during macrophage activation by phagocytic stimuli have unveiled links between the hydrolysis of either AA-containing PC or -PE and the formation of specific eicosanoid molecules [57]. During macrophage phagocytosis, the bulk of AA lost from membranes appears to originate from PC and PI, with seemingly little or no contribution from PE [57]. However, use of an inhibitor of CoA-IT that blocks the transfer of AA from PC to PE results in highly significant losses of AA from PE, indicating that during stimulation conditions AA is hydrolyzed from PE and the pools are rapidly replenished with AA from PC *via* transacylation reactions mediated by CoA-IT. Importantly, under these inhibitory conditions, the production of lipoxygenase metabolites increases, suggesting that the process of AA transfer between phospholipid classes does regulate the production of specific eicosanoids [57]. This opens the intriguing question of whether the synthesis of different eicosanoids is regulated by the action of cPLA$_2$α on different phospholipid pools, and whether the different accessibility of cPLA$_2$α to such pools can modify the course of the inflammatory response. In studies on the cPLA$_2$α-regulated eicosanoid response of bone marrow-derived mast cells, it was found that maturation of these cells is associated with phospholipid remodeling regulated in part by cPLA$_2$α, leading to a general decrease in AA-containing PC and PE. During the process of mast cell maturation in co-culture with fibroblasts, the AA released from mast cells by cPLA$_2$α is transferred to adjacent fibroblasts for the synthesis of anti-allergic prostaglandin E$_2$ [58].

The wide range of biological roles attributed to cPLA$_2$α has been extended by recent work implicating this enzyme in the selective production of lipid mediators during macrophage polarization to either M1 (pro-inflammatory) or M2 (anti-inflammatory) states. A recent study investigated the synthesis of lipid mediators released by macrophages treated with GM-CSF or M-CSF, which polarize the cells to M1 and M2 states, respectively [59]. While under unstimulated conditions both types of macrophages generate pro-resolving lipid mediators in a similar manner, upon cell stimulation with bacteria, M2 macrophages mobilize larger amounts of AA *via* increased cPLA$_2$α activation, and generate more leukotriene C$_4$, resembling in this regard the M2-like cells in lung allergy [59]. These differences may be due, at least in part, to differences in the localization/compartmentalization of AA-metabolizing enzymes, which determine substrate accessibility. Consistent with these results, more recent work has also highlighted the different lipid mediator signatures of macrophages responding to bacteria, depending on whether they have been polarized to M1 or M2 [60]. Still, much work remains to be carried out to clarify the compartmentalized regulation of enzymes participating in the synthesis of these lipid mediators, including cPLA$_2$α.

Previous studies demonstrated that cPLA$_2$α translocates to the phagosomal membrane during macrophage phagocytosis through mechanisms that, in humans, involve phosphorylation of the enzyme by c-Jun N-terminal kinases and membrane association *via* the cationic cluster of four lysine residues present at the catalytic domain of the enzyme (Fig. 2) [50,52,61–65]. More recently, it has been shown that the N-terminal C2 domain of cPLA$_2$α is sufficient to support FcR-mediated phagocytosis [66]. Importantly, overexpression of a cPLA$_2$α mutant without a complete catalytic domain, and therefore without enzymatic activity, rescues FcR-mediated phagocytosis in cells from *Pla2g4a*$^{-/-}$ mice [66]. Based on these data, the proposal was made that the C2 domain of cPLA$_2$α induces perturbation of the membrane phospholipid packing, potentially generating membrane bending that is necessary for phagosome formation in a manner independent of its enzymatic activity [66]. These studies are important in that they provide the first example of a biological function associated to cPLA$_2$α that does not depend on enzyme activity. It is also worth noting in this regard another recent study implicating cPLA$_2$α in the regulation of the tumor suppressor gene SIRT2 *via* mechanisms likely independent of the hydrolytic activity of the enzyme [67].

Related with the studies by Zizza et al. described above [66], work by Ward et al. [68] suggested that the C2 domain of cPLA$_2$α, which binds to zwitterionic membranes with high affinity in a Ca^{2+}-dependent manner, has a high membrane remodeling activity, producing dramatic changes in membrane curvature consistent with the role of cPLA$_2$α in the formation of the phagosome. Of note, cPLA$_2$α has long been recognized to regulate the formation of cytoplasmic lipid droplets under different conditions [69–72], by mechanisms likely implicating regulation of positive membrane curvature that is necessary for the nascent organelle to emerge from the endoplasmic reticulum [51].

Most recently, it has been described that cPLA$_2$α activity contributes to the phagosomal escape of *Mycobacterium tuberculosis* [73,74]. The enzyme appears to facilitate translocation of the microbe from the endosomal to the cytosolic compartment of human THP-1 macrophage-

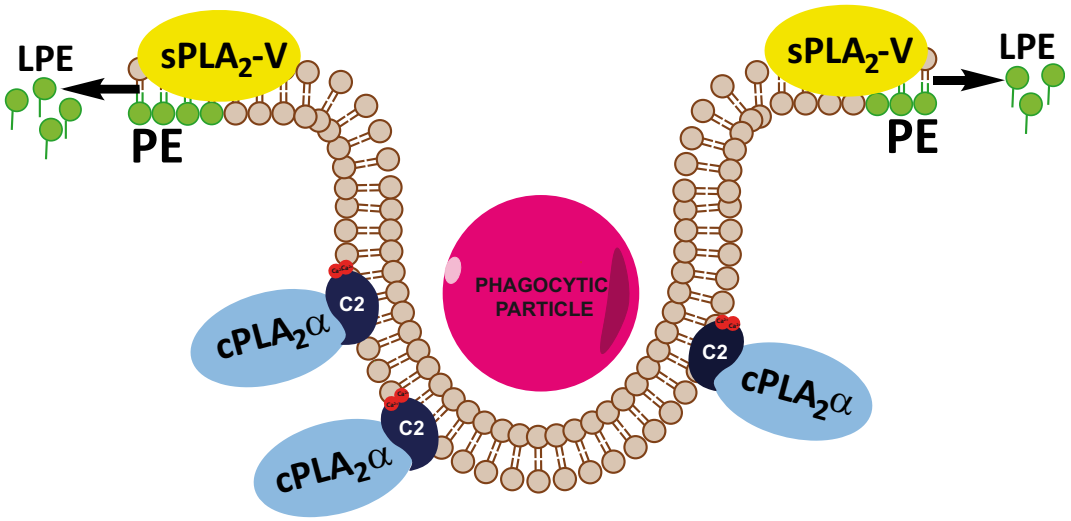

Fig. 2. Schematic representation of the involvement of PLA_2 enzymes in human macrophage phagocytosis. $cPLA_2\alpha$ translocates to the phagosomal membrane, and binding through the C2 domain assists in the formation of the phagosome itself. $sPLA_2$-V, presumably acting at plasma membrane, provides lysoPE molecules that may alter the structure and fluidity of a variety of microdomains, including lipid rafts, favoring oligomerization/interaction of phagocytic receptors.

like cells, allowing survival of the microorganism inside the cells. In addition, it was shown that prostaglandin E_2 helps to eliminate *M. tuberculosis* by increasing the apoptosis of infected macrophages. Apoptotic bodies are then captured by dendritic cells that mediate cross-presentation of *M. tuberculosis* antigens to $CD8^+$T cells to initiate adaptive responses [73,75]. Interestingly, lipoxin A_4 increases necrotic processes in infected macrophages, which helps bacteria to evade adaptive immunity [75].

Work by Slatter et al. [76] has unveiled a new biological function of $cPLA_2\alpha$ in metabolism, as a regulator of energy production by mitochondria. It was shown that, in thrombin-activated platelets, which produce large amounts of ATP *via* β-oxidation, $cPLA_2\alpha$ activation promotes fatty acid release and the subsequent β-oxidation of both eicosanoids and fatty acids. The rate of β-oxidation of eicosanoids is balanced with the rate of its generation, limited by $cPLA_2\alpha$, thus forming a positive feedback loop that serves to provide energy, dampen negative effects of excess of eicosanoids or the requirement of ATP as a kinase substrate [76].

Another interesting metabolic role for $cPLA_2\alpha$ was described in work by Peña et al. [77], where the enzyme was identified as an early key factor for adipocyte differentiation *in vitro*. Further, animals deficient in $cPLA_2\alpha$ that were subjected to a high fat diet show a reduced capacity to increase body weight and fat mass, highlighting the important role of $cPLA_2\alpha$ in regulating adipose tissue enlargement.

3. Ca^{2+}- Independent group VIA phospholipase A_2 ($iPLA_2$-VIA)

$iPLA_2$-VIA, also often abbreviated as $iPLA_2\beta$, is perhaps one of the PLA_2 enzymes for which more functions have recently been proposed. The enzyme was first found to participate in the regulation of lysophospholipid levels within the Lands' cycle [78–80]. Later work demonstrated that $iPLA_2$-VIA is a multifaceted enzyme with multiple roles in cell physiology and pathophysiology [35,81–84], being of special relevance in regulating intracellular signaling leading to insulin secretion [35], and phospholipid hydrolysis reactions during apoptosis [85–88].

Regarding eicosanoid production, $iPLA_2$-VIA appears, in general terms, not to play a major role in mediating this response in innate immunity and inflammation, as evidenced by the large number of studies highlighting the lack of effect of selective inhibition of the enzyme in stimulus-induced AA release in multiple immune cells [45,48,57,89–97]. Rather, the involvement of $iPLA_2$-VIA in the eicosanoid response appears to be restricted to specific conditions which depend on cell type, stimulus or lipid mediator to be formed [58,98–106]. In some of the latter studies, a certain preference of $iPLA_2$-VIA for cleaving AA-containing ether phospholipids was noted [105,106].

More recent work has demonstrated that $iPLA_2$-VIA participates in fatty acid remodeling reactions aimed at removing oxidized fatty acyl chains within cardiolipin molecular species [107]. This process, which can be regarded as a special case of the originally described phospholipid remodeling function of $iPLA_2$-VIA, and also agrees with previous observations that oxidation of membranes accelerates $iPLA_2$VIA-catalyzed fatty acid release [28,108], yields monolysocardiolipins that can be esterified back by new non-oxidized fatty acid. The reparation of oxidized phospholipids confers protection of β-cells against external injury [107]. It is interesting to note in this regard that the closely related enzyme $iPLA_2$-VIB ($iPLA_2\gamma$) has also been shown to play a major role in mediating the release of oxidized acyl chains from oxidized cardiolipins, leading to the production of second messengers and the removal of toxic products derived from oxidative stress in mouse myocardium [109].

A major open question in the field of lipid mediators is the molecular nature of the PLA_2 enzyme involved in the release of DHA and related omega-3 fatty acids from phospholipids as a first committed step for the generation of SPMs. Although by analogy with AA it is often assumed that $cPLA_2\alpha$ may serve this role, currently there is no direct evidence for this and, as discussed in the previous section, the *in vitro* specificity data are not revealing in this regard. Importantly, several recent studies provide evidence to suggest that $iPLA_2$-VIA may fulfill this role in brain. DHA is found at high concentrations in the *sn*-2 position of brain membrane phospholipids and is critical for maintaining normal brain structure, function and metabolism, participating in signal transduction, gene transcription, and membrane stability [110]. It has been shown that *Pla2g6*$^{-/-}$ mice exhibit disturbances in brain lipid composition and metabolism, which are associated with reduced incorporation of unesterified DHA from plasma into brain lipids and reduced esterified DHA concentrations in lipid classes [111–113]. Because DHA is the precursor of anti-inflammatory SPMs, the reduced brain DHA metabolism in the *Pla2g6*$^{-/-}$ mice may increase their vulnerability to neuroinflammation [114–117].

An unexpected result regarding the substrate selectivity of $iPLA_2$-VIA in cells has come from studies in mouse peritoneal macrophages [57]. Using pharmacological approaches and lipidomic strategies,

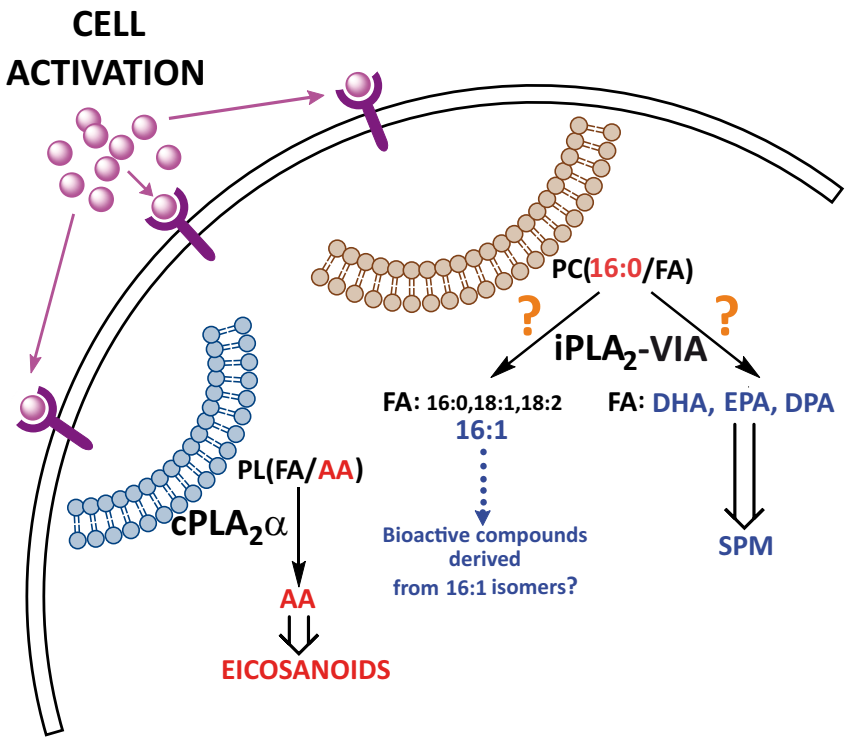

Fig. 3. cPLA$_2$α and iPLA$_2$-VIA exert their action on different phospholipid pools during cellular activation. cPLA$_2$α action leads to AA release and eicosanoid production. iPLA$_2$-VIA, by acting on phospholipids that do not contain AA but contain palmitic acid at the *sn*-1 position, may provide significant amounts of omega-3 free fatty acids for SPM synthesis, and perhaps also free 16:1 fatty acids which could be metabolized to yet undefined bioactive lipids.

evidence was obtained that cPLA$_2$α and iPLA$_2$-VIA act on different phospholipid pools. While the former regulates AA release and eicosanoid production, the later acts on phospholipids that do not contain AA. iPLA$_2$-VIA appears to selectively hydrolyze choline glycerophospholipids with palmitic acid at the *sn*-1 position, resulting in the production of palmitate-containing lysoPC, a lysophospholipid species with defined biological roles [85,118] (Fig. 3). Thus, iPLA$_2$-VIA also takes part in signaling cascades leading to the generation of lipid mediators. Interestingly, this selectivity of iPLA$_2$-VIA for PC containing palmitic acid at the *sn*-1 position had also been appreciated in a prior study utilizing iPLA$_2$-VIA-overexpressing HEK293 cells [119]. These two studies suggest more selectivity at the cellular level than observed for the *in vitro* selectivity of the pure recombinant human iPLA$_2$-VIA for the *sn*-1 fatty acid or phospholipid headgroup [24], pointing out the intriguing possibility that, in a physiological environment, iPLA$_2$-VIA could be compartmentalized in specific membranes enriched in palmitic acid-containing lipids.

Another interesting finding regarding substrate selectivity of iPLA$_2$-VIA in whole cellular systems stems from the observation that some of the major species hydrolyzed by the enzyme contain a 16:1 fatty acid at the *sn*-2 position [57,119], raising the possibility that iPLA$_2$-VIA may constitute a major pathway for the mobilization of this fatty acid from membrane phospholipids. The most abundant 16:1 fatty acid of mammalian cells is palmitoleic acid (16:1*n-7*), and there is strong evidence that this free fatty acid possesses anti-inflammatory activity, and suppresses hepatic steatosis and improves insulin sensitivity in murine models of metabolic disease [120,121]. Two isomers of palmitoleic acid, namely *cis*-7-hexadecenoic acid (16:1*n-9*) and sapienic acid (16:1*n-10*), were later identified in monocytes and macrophages [122,123] and, at least the first one displays strong anti-inflammatory activity as well. Differences in the distribution of the three 16:1 isomers among membrane phospholipids were detected [122], suggesting that not all of them may be mobilized in a similar manner during activation and that the multiplicity of effects initially attributed to palmitoleic acid may reflect the overlapping actions of several 16:1 isomers acting in concert at the same locations. It is also notorious the discovery of a novel family of anti-inflammatory lipids that results from the esterification of the hydroxyl group of a hydroxy fatty acid with another fatty acid (collectively termed “branched fatty acid esters of hydroxy fatty acids”, FAHFAs) [124–128]. The hydroxyfatty acids forming FAHFAs possess 16 or 18 carbon atoms. Little is yet known of their biosynthesis, but it has been shown that they are produced endogenously, thus it is tempting to speculate that the 16-carbon containing ones could derive from hydration of different isomers of 16:1 fatty acids.

Another important new result that has expanded the range of functions of iPLA$_2$-VIA in physiology and pathophysiology is its implication in macrophage polarization under stimulation conditions. Ashley et al. [129] described in peritoneal macrophages from *Pla2g6*$^{-/-}$ mice that the absence of iPLA$_2$-VIA facilitates macrophage polarization towards an anti-inflammatory M2 state, and modulates the expression of several enzymes involved in the synthesis of eicosanoid and reactive oxygen species. Conversely, the activation of genes involved in polarization to a pro-inflammatory M1 state is blunted in *Pla2g6*$^{-/-}$ macrophages. Overall, these results support a scenario where macrophage polarization may be dependent on signaling lipid molecules generated by PLA$_2$s [129].

Regarding novel roles for iPLA$_2$-IVA in metabolism, Deng et al. [130] recently demonstrated in *Pla2g6*$^{-/-}$ mice that the lack of the enzyme protects genetic obese mice from obesity and hepatic steatosis. The data support the notion that iPLA$_2$-VIA has a pathophysiological function *via* phospholipid remodeling which ultimately results in the depletion of polyunsaturated fatty acids from PC and PE, especially those molecular species that carry palmitic or stearic acids at the *sn*-1 position. Inactivation of iPLA$_2$-VIA reverses remodeling and establishes the return to normal homeostasis [130].

4. Group V phospholipase A$_2$ (sPLA$_2$-V)

An abundant body of work dating back from the 90's has documented the involvement of sPLA$_2$-V in AA mobilization and attendant eicosanoid production [131]. In general terms, sPLA$_2$-V acts by amplifying the action of cPLA$_2$α, which is the key enzyme in the process, *via* activity-dependent or -independent mechanisms. sPLA$_2$-V shows no

clear fatty acid preference [24], and is able to release other fatty acids from cells, *e.g.* oleic acid or linoleic acid [132–134], with regulatory features that are strikingly similar to those of AA release. From these results it can be inferred that sPLA$_2$-V may also be implicated in lipid metabolic pathways distinct from canonical AA signaling to exert its biological actions *in vivo*.

Several recent reviews have appeared covering different aspects of the sPLA$_2$ family of enzymes, including sPLA$_2$-V, and the interested reader is kindly directed to these for specific details [34,135–137]. It is important to remark here, however, that recent studies on sPLA$_2$-V suggest that some of the biological functioning of the enzyme is context- and even species-specific [34]. This is an important concept to take into account, because a considerable part of results regarding the role of sPLA$_2$-V in pathophysiology have come from studies in mice, and the availability of the sPLA$_2$-V knockout mouse model has provided much valuable insight [46,138]. However, the human enzyme differs from the mouse enzyme in at least one key aspect. In mouse peritoneal macrophages, sPLA$_2$-V translocates to the phagosome after ingestion of zymosan and regulates phagocytosis by mechanisms that may or may not depend on eicosanoid synthesis [139,140]. Under similar experimental conditions, however, the enzyme does not translocate to the phagosome in humans [61,62]. These data suggest that, at least in humans, the regulatory actions of the enzyme on the phagocytosis process itself occur at a level distinct from that of the phagosome, perhaps at the plasma membrane level. Interestingly however, it was recognized that the regulation of phagocytosis by sPLA$_2$-V in human and murine cells may actually lead to similar outcomes, *i.e.* in both systems sPLA$_2$-V favors the phagocytosis process, thus helps to resolve inflammation [139–141].

A recent lipidomic analysis determined that the increased expression of sPLA$_2$-V in interleukin-4–treated macrophages is selectively linked to increased levels of cellular ethanolamine lysophospholipids (LPE) [141]. These lipid molecules are necessary to support the elevated phagocytic response that these cells exhibit in response to both zymosan particles and live bacteria. The addition of exogenous LPE fully restores phagocytosis in sPLA$_2$-V–deficient cells, and overexpression of the enzyme produces a significant increase of the phagocytic capacity of the cells. It is possible that sPLA$_2$-V acts on the plasma membrane, and the accumulation of LPE alters the structure and fluidity of a variety of microdomains, including lipid rafts, favoring oligomerization/interaction of phagocytic receptors. Thus LPE may help develop further signaling, eventually favoring repair mechanisms and the return to homeostasis (Fig. 2). It has recently been discovered that ethanolamine lysoplasmalogens are, among LPE molecular species, the ones producing the largest effect (J. Rubio and J. Balsinde, unpublished data), pointing out again the importance of specific lipids in regulating innate immune functions. It is worth mentioning in this regard that another member of the sPLA$_2$ family, sPLA$_2$-IIF, was described earlier to cleave ethanolamine plasmalogens, generating lysoplasmalogen in keratinocytes, which is a biomarker of skin diseases [142]. Since ethanolamine phospholipids reside primarily in the inner leaflet of the plasma membrane, a scenario such as the one described above would be fully consistent with the large body of literature indicating that, after secretion of sPLA$_2$-V to the extracellular medium, the enzyme re-associates with the plasma membrane and, subsequently, is re-internalized by different mechanisms, including interaction of the enzyme with heparan sulfate proteoglycans [143] or caveolin-rich domains [144,145]. This could bring the enzyme into proximity with ethanolamine phospholipid pools at the inner leaflet to regulate specific cellular responses (Fig. 2) [131,146,147]. Thus, sPLA$_2$-V may act in an autocrine or paracrine fashion at different subcellular locations in the cell, depending on cell type and the nature of the activating stimulus.

Interestingly, anti-inflammatory actions for sPLA$_2$-V were also described in mice a few years ago in a model of autoimmune complex mediated arthritis [148]. A novel mechanism was delineated, whereby sPLA$_2$-V promotes phagocytosis of immune complexes by macrophages to ameliorate inflammation in autoimmune inflammatory arthritis. This function of sPLA$_2$-V appears to strikingly depend on enzymatic activity [148].

More recent studies have correlated sPLA$_2$-V with alternative macrophage activation (M2) in human and murine macrophages [149,150]. sPLA$_2$-V expression was induced during both human and mouse interleukin-4–mediated activation of macrophages *in vitro*, and its absence impaired macrophage activation *in vivo*. The elimination or depletion of sPLA$_2$-V from the macrophages of both species selectively reduces the expression of CCL22/CCL17 that determines effector T cell recruitment and eosinophilic inflammation. Collectively, these findings suggest that sPLA$_2$-V contributes to the Th2-dependent response for polarized activation of macrophages and that this function is conserved across species. Such a role is in intriguing contrast with earlier results suggesting that stimuli that polarize macrophages to M1 such as LPS, are also able to significantly up-regulate sPLA$_2$-V in several mouse tissues [151] and the transformed murine macrophage-like cell lines P388D$_1$ [152] and RAW264.7 (J. Rubio and J. Balsinde, unpublished results). As discussed elsewhere [34], it is possible that sPLA$_2$-V may be a bi-faceted enzyme with both pro- and anti-inflammatory ("Th2-prone") roles depending on conditions, cell types, and species.

Apart from its roles in innate immunity, sPLA$_2$-V is also suggested to participate in the progression of atherosclerosis. The enzyme is found in human atherosclerotic lesions, and hydrolyzes low-density-lipoprotein phospholipids in a way that the modified lipoproteins promote foam cell formation. However, there is not always an agreement on whether sPLA$_2$-V affects positively or negatively the cardiovascular process [153,154].

The hydrolysis of PC by sPLA$_2$-V seems to be favored in obesity, where adipocyte-released sPLA$_2$-V hydrolyzes excess PC of low density lipoproteins from animals fed a high fat diet, eventually protecting from hyperlipidemia. This links sPLA$_2$-V with energy metabolism, as seen in obese *Pla2g5*$^{-/-}$ mice and in human white adipose tissue, where *PLA2G5* expression inversely correlates with plasma low density lipoprotein levels [150]. The explanation is that the hydrolysis of low density lipoprotein particles produces unsaturated free fatty acids such as oleic or linoleic acid, which shift M1 to M2 macrophages or prevent palmitic acid-induced M1 macrophage polarization [150].

5. Group X phospholipase A$_2$ (sPLA$_2$-X)

Of all members of the sPLA$_2$ family of enzymes, sPLA$_2$-X is the one that shows the highest activity towards PC [155]. The enzyme is long known to release various fatty acids including AA and oleic acid, and increases prostaglandin E$_2$ production when added exogenously to phagocytic cells, suggesting a role for this enzyme in inflammation [156]. Later, its role in inflammatory lung diseases, both mouse and human, was defined [157–161]. More recently, using an inhaled allergen model, Nolin et al. [162] demonstrated that *Pla2g10*$^{-/-}$ mice are protected from developing allergic airway disease, altering the polarization of macrophages to an M2 state. These results point out to a critical function for sPLA$_2$-X in both the innate and adaptive immune response to inhaled allergens in human and mice. Other studies have described the involvement of sPLA$_2$-X in regulating the formation of cysteinyl leukotrienes in neutrophils by mechanisms involving cross talk with cPLA$_2\alpha$ [163,164].

Aside from the ability of sPLA$_2$-X to effect AA mobilization from a variety of cells [143,155,156], some recent studies have also described the ability of the enzyme to liberate DHA and other omega-3 fatty acids [133]. sPLA$_2$-X would effect the release of all omega-3 fatty acids, *i.e.* DHA, DPA and EPA preferentially over that of AA, placing this enzyme as another possible regulator of anti-inflammatory pro-resolving pathways [36]. In keeping with this notion, other works have attributed anti-inflammatory properties to sPLA$_2$-X in the development of atherosclerosis by limiting Th-1 responses or adipogenesis in murine models of obesity [165,166].

On the opposite side, sPLA$_2$-X has also been implicated in the pathology of cancer [167,168]. Human sPLA$_2$-X induces lipid droplet formation in *Ras*-driven MDA-MB-231 triple-negative breast cancer cells and promotes their survival during nutrient stress. It acts through the products of its enzymatic activity, most likely by providing mono- and polyunsaturated free fatty acids from cell membrane phospholipids for triacylglycerol synthesis that favor lipid droplet formation and reduces the requirement for *de novo* lipogenesis, protecting the cell against lipotoxicity and nutrient deprivation [167,168].

6. Other phospholipase A$_2$s

Oxidized phospholipids are formed from unsaturated acyl residues under oxidative stress in lipid membranes [169,170]. Oxidized phospholipids are frequently found in vascular tissues and lipoproteins, and usually contain an oxovaleroyl or glutaroyl residue at the *sn*-2 position, which result from the truncation and oxidation of an AA or EPA residue at C5. Traditionally, two PLA$_2$ enzymes were thought to hydrolyze truncated phopholipids, namely PAF acetylhydrolase I (group VIIA PLA$_2$), which is associated to liproproteins, and PAF acetylhydrolase II (group VIIB PLA$_2$), which acts intracellularly. Recent work has demonstrated that a third PLA$_2$, the lysosomal PLA$_2$ (group XV PLA$_2$) is also able to cleave oxidized phospholipids, thus uncovering a new catabolic pathway for the clearance of these molecules [171].

Recent work by Shimanaka et al. [172] has unveiled a novel and unexpected role for PAF acetylhydrolase II in regulating the production of a novel class of omega-3 epoxides in mast cells with key roles in mast cell activation and anaphylaxis. These epoxy omega-3 fatty acids are stored as esterified forms in membrane choline glycerophospholipids. Using bone marrow-derived mast cells from *Pafah2*$^{-/-}$ mice, it was demonstrated that PAF acetylhydrolase II is the specific enzyme that excises the epoxides away from the membrane. This way, PAF acetylhydrolase II initiates a novel signaling cascade mediated by epoxy omega-3 mediators that optimizes FcεRI-dependent mast cell activation [172].

Novel functions for other sPLA$_2$s have been described based on the lipid that they generate. sPLA$_2$-IIE acts preferentially on minor lipoprotein phospholipids, phosphatidylserine (PS) and PE [150]. sPLA$_2$-IID has been found to release DHA from PE in lymph node membranes, suggesting that this enzyme may also constitute another “resolving sPLA$_2$” that ameliorates inflammation through mobilizing DHA-derived pro-resolving lipid mediators [173]. Conversely, sPLA$_2$-IIA has recently been described to target phospholipids in extracellular mitochondria that are released from activated platelets or leukocytes to accumulate at inflamed sites, thereby amplifying inflammation [174].

7. CoA-independent transacylation reactions

The most common forms of membrane glycerophospholipids contain two acyl chains attached to the *sn*-1 and *sn*-2 positions of the glycerol backbone by ester bonds. However, there are glycerophospholipids that possess an *sn*-1 ether bond instead of an ester bond. Additionally, some of these ether-containing phospholipids also possess a *cis* double bond that is conjugated with the ether oxygen, *i.e.* forming a vinyl ether (Fig. 4). These phospholipids are called plasmalogens. In humans, plasmalogens constitute about 20% of total phospholipid content [175], but their biological roles are still to be fully recognized. Because of the lack of a carbonyl group at the *sn*-1 position, plasmalogens allow for a tighter packing of phospholipids in the membrane, which results in decreased membrane fluidity, and favor the formation and stabilization of membrane lipid raft domains with key roles in cellular signaling. Plasmalogens are also thought to act as endogenous antioxidants [175,176]. Only two major kinds of plasmalogens are found in mammalian cells, *i.e.* those containing either choline or ethanolamine as headgroups [177,178]. Inositol-containing plasmalogens have also been described but their levels are exceedingly low [179]. While heart contains relatively high amounts of choline plasmalogens, ethanolamine plasmalogens are particularly abundant in innate immune cells such as monocytes and macrophages. Notably, in these cells, practically only polyunsaturated fatty acids of both the omega-6 and omega-3 series are to be found at the *sn*-2 position of ethanolamine plasmalogens, with AA being the most prevalent one (Fig. 4). Owing to such fatty acid composition, the importance of this class of lipids to PLA$_2$-regulated pathways leading to generation of lipid mediators has long been recognized.

Mammalian cells contain significant amounts of a relatively lesser known enzyme that shows marked specifity for ether lipids containing AA and other 20–22 carbon fatty acids. This enzyme is called CoA-independent transacylase (CoA-IT), and transfers polyunsaturated moieties of 20–22 carbons, typically AA, from diacyl PC species to ether phospholipids, particularly the ethanolamine plasmalogens. This reaction is considered of special relevance not only for the maintenance of membrane homeostasis but also for ensuring the appropriate distribution of AA among the various phospholipid pools for the execution of PLA$_2$-dependent responses during immune cell activation [15,25,93,178,180–187]. Thus, CoA-IT is regarded as a key enzyme for the regulation of polyunsaturated fatty acid mobilization reactions in major immunoinflammatory cells. The rapid remodeling of AA moieties to ethanolamine plasmalogens during cell stimulation explains why in many instances, when measuring AA mobilization by mass in activated cells, no changes in the AA content of PE molecular species is observed, despite PE constituting the richest AA-containing class. The CoA-IT reaction prevents a decline of AA in the cellular amount of PE during cellular stimulation by channeling AA to PE from PC [2,54,55,57].

The CoA-IT sequence is presently unknown, making it one of the 1078 orphan enzymes currently listed in the ORENZA database (EC 2.3.2.147) [188]. Thus, presently the only way to study of CoA-IT is by measuring its enzyme activity or by pharmacological means [57,189–192]. The importance of CoA-IT in regulating the proper distribution of AA within phospholipids appears so relevant that, when its activity is blunted, the profile of eicosanoids generated by mouse peritoneal macrophages under activation conditions changes [57]. By directing AA from PC towards PE, CoA-IT modulates the relative amount of lipoxygenase products formed, thus suggesting that certain cellular AA phospholipid pools are selectively linked to the formation of specific eicosanoids [57]. This concept, first suggested by the work of Chilton in neutrophils [193] implies the existence of a third regulatory step of the eicosanoid biosynthetic response, *i.e.* at the level of fatty acid compartmentalization within the cell. CoA-IT, by helping to place precursor fatty acids in the appropriate cellular pools decisively influences the eicosanoid response because not all these pools may be equally accessible to the relevant PLA$_2$ involved.

CoA-IT is not a PLA$_2$ in a strict sense because it does not generate a free fatty acid as a product, but it does cleave the *sn*-2 position of a phospholipid. This has led to the consideration of whether CoA-IT is actually a PLA$_2$ “in disguise”, *i.e.* that the CoA-IT reaction represents just an uncharacterized activity of an otherwise described PLA$_2$ enzyme. As a matter of fact, some well characterized PLA$_2$s, *e.g.* cPLA$_2$α or iPLA$_2$-VIA, exhibit Ca^{2+}-independent transacylase activity *in vitro* [16]. Early work in macrophages utilizing PLA$_2$ inhibitors of known specificity failed to relate CoA-IT activity to any of the PLA$_2$ group types that had been characterized at that time (iPLA$_2$-VIA, cPLA$_2$α, or sPLA$_2$-V) [93]. Consistent with these results, a subsequent study confirmed that neither cPLA$_2$α, nor iPLA$_2$-VIA nor sPLA$_2$-V were involved in AA phospholipid remodeling in peripheral blood T cells [181]. More recent studies have contemplated the possibility that CoA-IT activity may belong to cPLA$_2$γ (group IVC PLA$_2$) [194–196]. Despite being a group IV enzyme, cPLA$_2$γ is actually Ca^{2+}-independent because it lacks the C2 domain present in the other group IV members [16]. However, the lysophospholipase activity of cPLA$_2$γ is considerably higher than its CoA-independent transacylation activity, which casts doubt as to whether this enzyme is actually responsible for moving AA from PC to

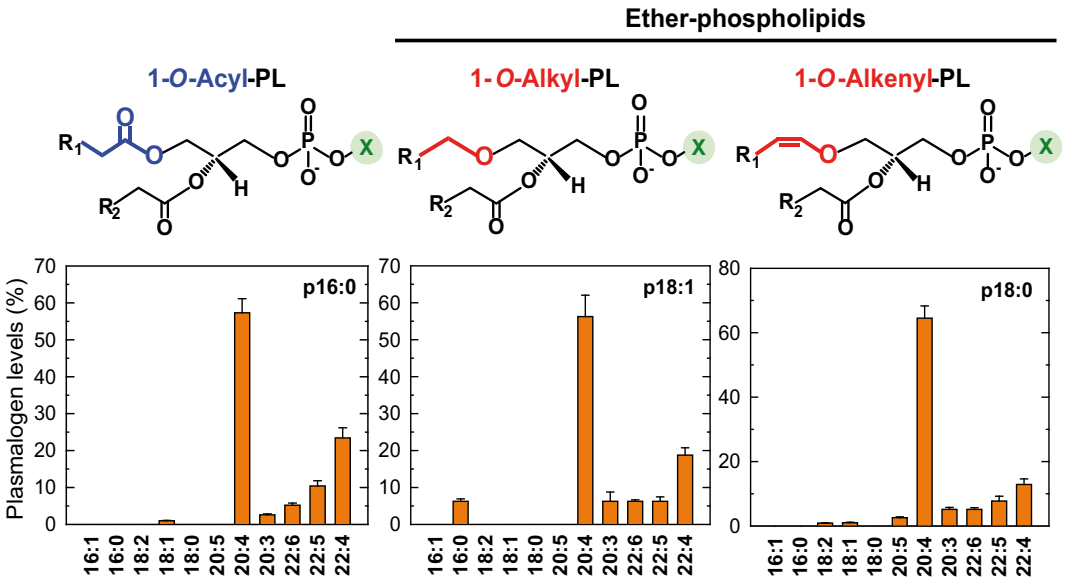

Fig. 4. Representative structures of 1-acyl, 1-alkyl, or 1-alkenyl glycerophospholipids (upper panel). 1-Alkenyl glycerophospholipids are called plasmalogens and annotated with a "p" before *sn-1* hydrocarbon chain abbreviation. In peritoneal macrophages the fatty acid composition at *sn*-2 for the three major plasmalogens (p16:0, p18:1 and p18:0) is markedly enriched with AA (20:4) (bottom panels). A lipid extract from approximately 2×10^6 mouse peritoneal macrophages was analyzed by liquid chromatography coupled to triple quadrupole mass spectrometry in MRM mode. Results are shown as means ± SE of three independent experiments with incubations in duplicate.

PE in cells [194,195].

Because of the lack of sequence, current knowledge on the cellular regulation of CoA-IT is scarce. However, recent work has suggested an interesting new role for CoA-IT in regulating the extent of the AA mobilization response in primed macrophages. Bacterial lipopolysaccharide (LPS) is a poor trigger of AA mobilization in macrophages but has the capacity to greatly increase the response upon a subsequent cellular stimulation. Gil-de-Gómez et al. [197] recently showed that LPS priming of macrophages is strikingly associated with an increased hydrolysis of ethanolamine plasmalogens by cPLA$_2$α, which is due, at least in part, to diminished recycling of AA into this particular species *via* CoA-IT-mediated transacylation reactions. Reduced CoA-IT activity after LPS priming could bear important pathological consequences because it may lead to excessive damage arising from an exacerbated production of eicosanoids subsequent to the increased availability of free AA [197]. An important unanswered question that stems from these observations is whether the priming effect is exerted directly on the CoA-IT enzyme itself or rather by impacting on an unrecognized effector that regulates upstream events such as the proper access of the enzyme to its substrate. The latter scenario would be analogous to that described for CoA-IT regulation of platelet-activating factor synthesis in human neutrophils, which depended upon substrate availability, not increased enzyme activity [198].

Another important regulator of CoA-IT-mediated reactions that has recently been unveiled is the cellular level of esterified AA in membranes. It has been known for some time that phospholipid AA remodeling is much faster in cell lines than that in their counterpart physiologic cells. For example, complete AA transfer from PC to PE generally takes hours in murine macrophages or human monocytes, while it takes only minutes in the murine macrophage-like cell line P388D$_1$ or the human monocyte-like cell line U937 [15,25,189,197,199,200].

Astudillo et al. [189] demonstrated that cellular AA levels determine the amount of CoA-independent transacylase activity expressed by cells; the lower the levels of cellular AA, the higher the extent of cellular CoA-IT activity [189]. The mechanism through which this occurs remains to be elucidated but, since simply enriching the cells with AA reduces the measurable CoA-IT activity of homogenates, it seems likely that an unidentified AA metabolite or AA-containing phospholipid that is present in the AA-enriched cells may act to regulate the expression levels of CoA-IT [189].

8. Concluding remarks

Much progress has been made in recent years to understand the cellular regulation of the selective hydrolysis of membrane phospholipids by PLA$_2$s. Still, the different activation conditions and the accessibility to different pools in the cell may lead to the production of yet unidentified lipid mediators that participate in crucial pathophysiological events. It is important to emphasize that PLA$_2$ represents the very first step of signaling pathways that involve lipid mediators which act *per se* or may be further metabolized to other bioactive compounds. The definition of molecular mechanisms governing the catalytic activity and substrate preference of the various cellular PLA$_2$s under stimulation conditions is a very significant yet still unexplored field.

Transparency document

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

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