Phospholipase A_2, Lipid Signaling and Lipidomics in Innate Immunity and Inflammation

The Eicosanoid Research Division*

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*https://www.balsinde.org
September 26, 2026

Version 5.0

There is some discrepancy as to what really is the kick-off date of the Eicosanoid Research Division (or the Eicosanoid Laboratory, as it came to be known first). Truth be told, the thing took its first *official* steps in September 2000, with my definitive arrival in Valladolid. Beginnings are always difficult, and mine in the unofficial capital of Old Castile was no exception. Because of this and a few other things, the details of which I will spare the reader, I normally set the beginning of our scientific adventures in Castile just one year later, in the fall of 2001. At that time, something resembling a biomedical research lab was finally available and a few people were around to start the journey along. Our subject matter, obviously, lipids and all things lipids. Why always lipids, you may ask. Good question. For the moment being, let's say that lipids play fundamental roles in the regulation of cell signaling, and that imbalances in lipids and lipid-mediated signaling cause a large number of diseases, including type 2 diabetes, Alzheimer, arthritis and atherosclerosis. With that in mind, it should become obvious that one of the first steps we have to take in the direction of curing these diseases is to identify the lipids that are involved and to determine what they specifically do.

Many signaling lipids are generated by phospholipases such as phospholipase A_2, which produces lysophospholipids and free fatty acids such as arachidonic acid. Further, many of the enzymes involved in the *de novo* pathways of lipid biosynthesis are also implicated in signaling. While our scientific interests include a comprehensive characterization of the roles played by both biosynthesis and remodeling pathways to overall cell signaling, our current research focuses primarily on the enzymes involved in maintaining the composition and levels of different fatty acids in biological membranes, i.e. phospholipases and acyltransferases. It is becoming clear that the phospholipid composition of biological membranes is very dynamic and that cells likely sustain many biological functions with different but somehow equivalent lipid compositions rather than a single one. Taking this concept a bit further, one could speculate that perhaps it is that, when the different lipid classes and subclasses interact to form a biological membrane, not all concentrations of each species are possible or permitted (or required). Something like quantum lipid states? Fascinating indeed. In our laboratory we combine a range of chemical, biochemical, pharmacological, and molecular cell biology techniques to study lipid metabolism and signaling in physiology and pathophysiology. Within this context, our current goals can be summarized into five points, which are described below. This report covers the research activities of our lab from the beginning until December 2026.

(1) Cellular regulation of phospholipase A_2.

Phospholipase A_2 enzymes catalyze a key reaction in signaling, i.e. the release of arachidonic acid and other polyunsaturated fatty acids from the *sn*-2 position of cellular glycerophospholipids. The products of phospholipase A_2 action, free fatty acids and lysophospholipids may act as signaling molecules on their own,

and also serve as a precursors for the synthesis of the eicosanoids or platelet-activating factor. Our group has a long history in studying the mechanisms of regulation of phospholipase A_2 in resting and stimulated cells [reviews: 1–14]. Our work has highlighted the differential contribution of various phospholipase A_2s to the formation of cellular lysophospholipid pools, and the important role that group VIA phospholipase A_2 plays in this process [15–17]. This latter enzyme appears to serve multiple roles in cells, and delineating some of these has been the subject of many studies. Specifically, we have studied the involvement of group VIA phospholipase A_2 in modulating lysozyme secretion as well as its various roles in cell proliferation and apoptosis [18–21]. We have identified a hitherto unrecognized preference of this enzyme for choline phospholipids containing palmitic acid at the *sn-1* position [22]. This preference is found in cells but it is not clear in cell-free assays, which suggests a key role for cell compartmentalization in the regulation of group VIA cytosolic phospholipase $A_2\alpha$ activity under pathophysiological conditions. More recent work has shown that the enzyme is a major effector for the stimulated mobilization of two fatty acids that may possess anti-inflammatory activity, namely adrenic acid [23] and palmitoleic acid and its positional isomers [24–26].

Subcellular localization studies of various phospholipase A_2 forms have been conducted [27,28]. Various determinants and signaling events that regulate the subcellular localization of the arachidonate-specific cytosolic group IVA phospholipase $A_2\alpha$ have been described in detail. Among these, we have unveiled the role of a cationic cluster present in the catalytic domain of the protein in regulating membrane binding via interaction with anionic phospholipids. The involvement of phosphorylation reactions in regulating the localization of the enzyme to phagosomes has been characterized as well [29–33]. Further work has led to the identification of the cytoslic group IVA phospholipase A_2 as an early key factor for adipocyte differentiation in vitro, and in vivo during high fat diet-induced obesity [34].

Studies on the secreted group V phospholipase A_2 have shown that this enzyme is strongly upregulated in human macrophages by interleukin-4, but not by interferon-γ plus lipopolysaccharide. We found that the increased expression of the enzyme in interleukin-4-treated macrophages serves to regulate the cellular levels of ethanolamine lysophospholipids that are necessary to support the elevated phagocytic response that these cells exhibit [35]. These results raise the provocative idea that group V phospholipase A_2 may act as a bi-faceted enzyme in innate immunity and inflammation, playing either pro- or anti-inflammatory roles depending on conditions.

(2) **Signaling mechanisms involved in the bio-synthesis of eicosanoids by cells of the immune system.**

The eicosanoids are a large family of bioactive mediators that derive from the enzymatic oxygenation of arachidonic acid. The eicosanoids are biomedically important because they mediate all four signs of inflammation, namely heat, redness, swelling and pain. Controlling the formation of eicosanoids has been found to be of great benefit for the treatment of acute and chronic inflammatory diseases. We have extensively characterized the differences in arachidonate mobilization and eicosanoid metabolism by agonists acting via Toll-like receptors [36–38]. Overall, our results have provided support to a model whereby secreted group V phospholipase A_2 may contribute to the eicosanoid biosynthetic response in some cases, by increasing the activation of cytosolic group IVA phospholipase A_2 through amplification of phosphorylation cascades. This represents another instance of cross talk between secreted and cytosolic phospholipase A_2s. This is a concept that has been around for a long time but still remains poorly characterized in molecular terms. Regarding the interaction of exogenous secreted phospholipase A_2 forms with cells, we have identified a mechanism connecting endogenous cytosolic phospholipase A_2 with the exogenous group V enzyme via the formation of hydroperoxyeicosatetraenoic acid. This metabolite is produced by cells in a cytosolic phospholipase A_2-dependent manner, and appears to helps the secreted enzyme to properly act on the membrane [39]. More recently, we have used a secreted group IIA phospholipase A_2, isolated from snake venom to characterize in lipidomic terms its interaction with human cells [40,41]. Again much of the effects of group IIA phospholipase were found to involve the endogenous group IVA enzyme.

We have identified that lipin-1, a phosphatidate phosphatase enzyme residing on the surface of lipid droplets, may lie upstream group IVA phospholipase $A_2\alpha$, thus suggesting the existence of new and unexpected ways to regulate arachidonate mobilization and eicosanoid synthesis [42]. The lipin family of enzymes consists of 3 members, with one of them exhibiting 3 splicing variants. Aside from the aforementioned role for

lipin-1, it is not known whether other lipin proteins regulate the eicosanoid cascade and this is a possibility that needs to be explored. Importantly, these enzymes appear to play significant roles not only in regulating phospholipid metabolism [19] but also in key aspects of innate immunity and inflammation [review: 43]. These include: (i) the regulation of lipopolysaccharide signaling and systemic inflammation [44–47], (ii) the activation of the NLRP3 inflammasome [48], (iii) the development of inflammation-driven colon carcino-genesis [49], and (iv) the antiviral and anti-inflammatory responses to interferon [50].

(3) **Membrane fatty acid metabolism; incorporation into phospholipids and remodeling**.

The distribution of polyunsaturated fatty acids in cells is tightly regulated by a set of reactions of incorporation, remodeling and liberation of the fatty acids into, among and from phospholipids, respectively. These reactions ensure the proper distribution of the fatty acids within the various cellular phospholipid pools, which is important not only for membrane homeostasis but also for the execution of appropriate cell responses during physiological and pathophysiological activation. Our current work pays special attention to the interactions between n-3 and n-6 fatty acids, due to their importance as precursors of a large number of bioactive substances. Members of these two fatty acid families compete with each other for incorporation into the *sn*-2 position of membrane glycerophospholipids, which may provide a control point for regulating their cellular levels, and hence the amount of oxygenated products generated after stimulation. Our work has led to the discovery of the selective involvement of lysophosphatidylcholine acyltransferase 3 (LPCAT3) as a novel signal-regulated enzyme involved in arachidonic acid metabolism in human monocytes [51]. Also, inhibition studies of phospholipid fatty acid incorporation and remodeling at various points have shown increases in cellular free arachidonate levels that may conduct to cell death by apoptosis [52]. More recent studies aimed to characterize at the cellular level the different specificities of the CoA-dependent routes of fatty acid incorporation (acyl-CoA synthetases and CoA-dependent acyltransferases), as well as the subsequent remodeling of the fatty acids into various cellular pools by CoA-independent transacylases [53–56]. Results from these studies have raised the possible involvement of an ortholog of cytosolic group IVA phospholipase A_2, namely the group IVC enzyme (cytosolic phospholipase $A_2\gamma$) in phospho-lipid arachidonate remodeling [56]. The amount of cellular coenzyme A-independent transacylation activity that this enzyme accounts for is not known at present. Work is currently in progress to clarify this point, and also whether the enzyme is constitutively active or its activity increases after agonist stimulation.

Significant advances have been made through the use of plasmalogen-deficient macrophage-like cells. Despite the well known fact that ethanolamine plasmalogens are enriched in arachidonic acid and other polyunsaturates, and that they constitute major substrates for coenzyme A-independent transacylation reactions, our recent work has suggested that cells deficient in plasmalogens remodel arachidonate between phospholipids just as well as normal cells [56]. Thus it seems that overall phospholipid arachidonate remodeling is essentially independent of the amount of plasmalogen present in the cells. Compartmentalization of arachidonate in innate immune cells may instead depend on the relative distribution of the fatty acid among classes (ethanolamine versus choline versus inositol headgroups) rather than on specific molecular species within classes (i.e., alkenyacyl versus alkylacyl versus diacyl species) [56]. It is quite interesting that the incorporation of various monohydroxylated derivatives of arachidonate (5-, 12-, and 15-hydroxyeicosatetratenoic acids, HETEs), which are produced by the action of different lipoxygenases, appears to follow the same scheme; the class-specific pattern of HETE incorporation (ethanolamine versus choline versus inositol) is preserved even when ether phospholipids are absent, indicating that headgroup identity, rather than phospholipid subclass composition (alkenylacyl, alkylacyl, or diacyl species), primarily determines HETE distribution [57].

While the finding that cellular plasmalogen status does not influence arachidonate remodeling was clearly unanticipated, our studies with plasmalogen-deficient cells have uncovered essential roles for ethanolamine plasmalogens in regulating other macrophage responses such as phagocytosis [58] and priming with bacterial lipopolysaccharide [59]. Regarding the former, it seems likely that ethanolamine plasmalogens contribute to a substantial part of the ethanolamine lysophospholipid pool that is necessary to maintain the phagocytic response of macrophages [35], as mentioned in preceding paragraphs. From these data, an interesting scenario emerges, suggesting that lipopolysaccharide priming of macrophages slows down the coenzyme A-independent movement of arachidonate between phospholipids. This results in a reduced transfer of arachidonate from choline

to ethanolamine phospholipids. Higher amounts of the fatty acid in choline phospholipids in the primed cells would mean that the phospholipase is able to mobilize greater amounts of the free fatty acid from this phospholipid class after a second stimulation, due to compartmentalization of the fatty acid [59]. This scenario nicely reconciles the observations that choline phospholipids are not the major arachidonate-containing phospholipid class in macrophages, yet they seem to constitute the major source of free fatty acid that is specifically used for prostaglandin E_2 synthesis during the acute stimulation of macrophages with phagocytic stimuli [55].

In other series of experiments we have found that the extent to which arachidonate moves between phospholipids appears to depend on the nature of the triggering stimulus. Studies comparing the effects produced by native zymosan (primarily actin through receptors for β-glucan) versus opsonized zymosan (primarily acting through Fc receptors), have indicated that the latter induces remodeling of arachidonate at a slower rate [60]. Following a similar rationale to that described in the preceding paragraph, this results in greater availability of the fatty acid in choline phospholipids, and hence in a stronger arachidonate release response [60]. Thus, a reduced CoA-IT rate after cell stimulation will increase the amount of free arachidonate available for eicosanoid synthesis. Conversely, an increased rate of arachidonate transfer by CoA-IT diverts the fatty acid to phospholipid pools and decreases its availability for eicosanoid production. Collectively, our research supports the general concept that differential stimulation of phagocytic cells promotes selective lipid turnover and, therefore, the appearance of specific lipid signatures for each activation condition.

(4) **Biosynthesis and degradation of lipid droplets during cellular activation.**

Lipid droplets are dynamic cytoplasmic structures which, among many things, may function as docking platforms for a number of enzymes involved in lipid signaling [reviews: 8,11]. We have described the regulation of lipid droplet biosynthesis by various members of the phospholipase A_2 family of enzymes as well as the differential involvement of various lipid metabolic pathways in signal-regulated lipid droplet formation under proinflammatory conditions [61–64]. Our most significant results in this area of research suggest that phosphorylation activation of group IVA phospholipase $A_2\alpha$ by multiple kinases drives lipid droplet formation in cells possibly by facilitating biogenesis of this organelle, not by regulating neutral lipid synthesis [64].

We have shown that human monocytes exposed to free arachidonic acid, a secretory product of endothelial cells, acquire a foamy phenotype which is due to the accumulation of cytoplasmic lipid droplets with high arachidonate content [64,65]. In defining the origin of the fatty acids accumulating in the neutral lipids of these lipid droplets (i.e. increased de novo fatty acid synthesis *versus* uptake of exogenous fatty acid), we made the unexpected finding that they contained significant amounts of an unusual fatty acid, *cis*-7-hexadecenoic acid (16:1*n-9*), a positional isomer of palmitoleic acid. The fatty acid shows significant anti-inflammatory activity *in vitro* and *in vivo* and might be regarded as a biomarker for early detection of cardiovascular disease [65]. Since *cis*-7-hexadecenoic acid accumulates in foamy monocytes in response to free arachidonic acid, a pro-inflammatory mediator, it is conceivable that metabolic changes underlying the formation and accumulation *cis*-7-hexadecenoic acid fatty acid into specific lipid classes are instrumental in showcasing effector functions of monocytes and macrophages toward the re-establishment of homeostasis during the course of inflammation processes. Further work showed that phagocytic cells contain at least a third 16:1 positional isomer, namely *cis*-6-hexadecenoic acid (sapienic acid, 16:1n-10) [66].

Using cells treated with arachidonate to induce lipid droplet formation, we also investigated whether the arachidonic acid present in neutral lipids is mobilized during activation conditions, and thus contributes to lipid mediator formation. Our results in this regard suggest that this is not the case. Using cells of either human or murine origin, we found that virtually all of the fatty acid that is released from activated cells comes from membrane phospholipids [67,68]. An intriguing possibility to consider is that arachidonate entry into neutral lipids may serve as an expandable storage pool to protect the cells from the toxicity of the fatty acid and/or to limit inflammation by reducing the amount of free fatty acid available for eicosanoid synthesis. The possibility should also be contemplated that the arachidonate present in neutral lipids within the lipid droplet may be mobilized to replenish empty phospholipid pools, as it is known that leukocytes are endowed with all the machinery required to transfer arachidonate from triacylglycerol to phospholipids via CoA-dependent reactions.

(5) **Lipidomics and metabolipidomics; identification**

and quantification of cellular lipidomes by mass spectrometry.

The development of mass spectrometry techniques for the detection and analysis of lipids at a global scale provides us with a unique opportunity to characterize in detail the changes occurring in lipid metabolism as a consequence of cell activation [reviews: 6,7]. Since multiple lipid metabolic pathways are known to be activated by receptor stimulation of cells, one of the major goals of our research in this area is to determine the origin and identity of the individual phospholipid molecular species that are produced under different conditions, as a first step to address their biological roles in cells. In the context of these studies, we described a number of novel arachidonate-containing lipids, the levels of which increase during cell activation [69,70]. A remarkable finding from these studies was the discovery of the novel molecular species 1,2-diarachidonoyl-*sn*-glycero-3-phosphoinositol as a major but transient reservoir of arachidonic acid. The molecule appears to be produced by sequential remodeling of a preexisting phosphatidyl-inositol molecule first at position *sn*-2 and then at *sn*-1 with arachidonate, and could be involved in modulating innate immune responses such as superoxide anion production or secretion of antimicrobial hydrolases [71].

Other arachidonate-containing lipids have been identified in a stimulus- and cell type-dependent manner. A potentially interesting one is 1-palmitoleyl-2-arachidonoyl-*sn*-glycero-3-phosphoethanolamine, which is not present in resting monocytes but accumulates rapidly under receptor stimulation [70]. Again, these studies support the idea that changes in lipid content upon activation may be stimulus-specific, and also that cellular activation includes both common and stimulus-specific markers. Similar work has been conducted with lipids containing adrenic acid, the two-carbon elongation product of arachidonic acid [23,72]. Our data in this regard suggest that differences exist between the cellular mechanisms regulating the availability of adrenic acid and arachidonic acid, albeit complexities may arise from the existence of an active conversion/retroconversion cycle between the two fatty acids.

More recently, we also addressed the distribution of another major polyunsaturated fatty acid in murine macrophages, i.e. the n-3 fatty acid docosahexaenoic acid (22:3n-6). The data show a marked abundance of this fatty acid in ether phospholipids. Similar to arachidonic acid, docosahexaenoic acid is mobilized in activated cells primarily form choline and inositol phospholipid species, with little or no contribution of ethanolamine phospholipids [73]. Remarkably, a unique species that was barely detected in resting cells, 1-arachidonoyl-2-docosahexaenoyl-sn-glycero-3-phosphoinositol, was found to markedly increase after macrophage stimulation [73]. The biological significance of this species, if any, remains to be determined.

Lipidomic analyses of the distribution of palmitoleic content in phagocytic cells have demonstrated that most of this fatty acid resides in one single phospholipid species, namely 1-palmitoyl-2-palmitoleoyl-sn-glycero-3-phosphocholine [24,66]. This is striking, and prompted us to investigate whether, similar to other choline phospholipid species, this palmitoleate-containing species may have biological activity on its own. The outcome of our studies suggested that this may be indeed the case, and the whole phospholipid directly regulates macrophage activation. It suppresses NF-κB signaling, reprograms gene expression, and promotes a shift toward an anti-inflammatory, M2-like phenotype that enhances phagocytic capacity. These effects are preserved in ether analogs resistant to phospholipase-mediated hydrolysis, confirming that the release of free palmitoleate is not required [74].

In addition to the above, in activated macrophages, small amounts of palmitoleic acid are liberated from phosphatidylcholine at small amounts by the action of calcium-independent group VIA phospholipase A_2, or iPLA$_2$β [24,26]. Interestingly, a fraction of the liberated palmitoleate is utilized in phospholipid fatty acid remodeling reactions to enrich inositol lipids with this fatty acid [26]. The transfer of palmitoleic acid to inositol phospholipids during macrophage activation is particularly striking from a biochemical point of view, as it involves the participation of two phospholipase A_2 enzymes acting separately but converging to generate lipid diversity. cPLA$_2$α generates the inositol lysophospholipids that will accept the 16:1 fatty acids being released primarily from phosphatidylcholine by iPLA$_2$β [26].

We have also initiated work to characherize the formation of FAHFA (fatty acid esters of hydroxy fatty acids) and the effect that cellular activation may have on certain species. Our work in this area has described the increased formation of a single palmitoleate-containg FAHFA species in activated macrophages [24]. While the biological significance of this species, if any, is unknown, its formation raises the intriguing possibility that part of the biological activity of palmitoleic acid may also derive

from its conversion to other lipids. Working with samples of human colon cancers we have found some connection between FAHFA levels and cell death, which led us to suggest that FAHFA formation in cancer cells could function as a buffer system that sequesters the hydroxy fatty acids into an inactive form, thereby avoiding apoptosis [75].

Finally, our expertise in lipidomics has made it possible for us to interact with other research groups, and these interactions have led to collaborative studies that focus on the identification of lipid alterations in various models of disease, including caveolin-1 deficiency [54,76–79], intestine epithelium permeability [80], metabolic disorders [81–91], cancer [92,93], spinal cord injury [94], platelet activation and aggregation [95], and sepsis and infection [96–98]. Several other lipidomic analyses are currently being carried out in our laboratory under various collaborative agreements.

Incidentally, we are accumulating a growing number of editorial introductory notes for special issues [10,99,100].

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