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Review

Compartmentalized regulation of lipid signaling in oxidative stress and inflammation: Plasmalogens, oxidized lipids and ferroptosis as new paradigms of bioactive lipid research

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ABSTRACT

Perturbations in lipid homeostasis combined with conditions favoring oxidative stress constitute a hallmark of the inflammatory response. In this review we focus on the most recent results concerning lipid signaling in various oxidative stress-mediated responses and inflammation. These include phagocytosis and ferroptosis. The best characterized event, common to these responses, is the synthesis of oxygenated metabolites of arachidonic acid and other polyunsaturated fatty acids. Major developments in this area have highlighted the importance of compartmentalization of the enzymes and lipid substrates in shaping the appropriate response. In parallel, other relevant lipid metabolic pathways are also activated and, until recently, there has been a general lack of knowledge on the enzyme regulation and molecular mechanisms operating in these pathways. Specifically, data accumulated in recent years on the regulation and biological significance of plasmalogens and oxidized phospholipids have expanded our knowledge on the involvement of lipid metabolism in the progression of disease and the return to homeostasis. These recent major developments have helped to establish the concept of membrane phospholipids as cellular repositories for the compartmentalized production of bioactive lipids involved in cellular regulation. Importantly, an enzyme classically described as being involved in regulating the homeostatic turnover of phospholipids, namely the group VIA Ca^{2+}-independent phospholipase A_2 ($iPLA_2\beta$), has taken center stage in oxidative stress and inflammation research owing to its key involvement in regulating metabolic and ferroptotic signals arising from membrane phospholipids. Understanding the role of $iPLA_2\beta$ in ferroptosis and metabolism not only broadens our knowledge of disease but also opens possible new horizons for this enzyme as a target for therapeutic intervention.

1. Introduction

The innate immune system is the major contributor to acute inflammation induced by microbial infection or tissue damage, and is also essential for the activation of acquired immunity [1,2]. Innate immune cells include professional phagocytic cells such as neutrophils, macrophages and dendritic cells, and also non-professional phagocytic cells such as epithelial cells, endothelial cells, and fibroblasts. Germline-encoded pattern recognition receptors (PRRs) present in all of these cell types sense the presence of microorganisms by recognizing structures conserved among microbial species, the so called pathogen-associated molecular patterns (PAMPs). PRRs are also able to recognize

Abbreviations: AA, arachidonic acid; AdA, adrenic acid; ACSL, long-chain acyl-CoA synthetase; CoA-IT, CoA-independent transacylase; COX, cyclooxygenase; DAG, diacylglycerol; eoxPL, enzymatically oxidized phospholipids; HETE, hydroxyeicosatetraenoic acid; HPETE, hydroperoxyeicosatetraenoic acid; LOX, lipoxygenase; LysoPC, choline lysoglycerophospholipid; LysoPE, ethanolamine lysoglycerophospholipid; LysoPI, lysophosphatidylinositol; LPCAT3, lysophosphatidylcholine acyltransferase 3; LPIAT, lysophosphatidylinositol acyltransferase; MBOAT, membrane-bound O-acyltransferase; NET, neutrophil extracellular trap; oxPL, oxidized phospholipids; PC, choline glycerophospholipid; PE, ethanolamine glycerophospholipid; PI, phosphatidylinositol; PL, phospholipid; PLA_2, phospholipase A_2; $iPLA_2\beta$, group VIA calcium-independent phospholipase A_2; $cPLA_2\alpha$, group IVA cytosolic Ca^{2+}-dependent $PLA_2\alpha$; $cPLA_2\gamma$, group IVC cytosolic phospholipase $A_2\gamma$; PAMPs, pathogen-associated molecular patterns; PRRs, pattern recognition receptors; PS, phosphatidylserine; PUFA, polyunsaturated fatty acid; ROS, reactive oxygen species; TLR, Toll-like receptors.

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endogenous molecules released from damaged cells, termed damage associated molecular patterns (DAMPs). Currently, four different classes of PRR families have been identified; Toll-like receptors (TLRs), C-type lectin receptors (CLRs), retinoic acid-inducible gene (RIG)-I-like receptors (RLRs), and NOD-like receptors (NLRs). The sensing of PAMPs or DAMPs upregulates the transcription of genes involved in inflammatory responses, such as cytokines, type I interferons, chemokines, and other antimicrobial proteins. In this scenario, the amplification of the inflammatory response is made possible to a large extent by the continued production of lipid mediators. Together, proteins and lipid mediators favor the recruitment of additional immune cells and the initiation of the acquired immunity [3–8]. In addition, equally important is the resolution of inflammation and adequate limitation of the response to avoid excessive inflammatory responses. Lipid mediators actively participate in the execution of resolution events, where phagocytosis and apoptosis play key roles [9–11]. Thus, during the development of pro- and anti-inflammatory processes, substantial rearrangement of lipid metabolic pathways and energetic programs take place, which participate decisively in the different polarization states of phagocytic cells [12,13]. Such is the importance of bioactive lipids that an imbalance in lipid biosynthesis or metabolic regulation is key for the development of a large number of chronic inflammation diseases, ranging from heart disease, to stroke, arthritis, diabetes and Alzheimer disease [14,15].

Adequate reorganization and reprogramming of lipid metabolism thus appears as an indispensable event for achieving an effective inflammatory response. However, there still exists a significant lack of knowledge on the enzymatic regulation, synthesis, release, remodeling and mechanisms of action of bioactive lipid mediators that cooperate along the course of the immune response. It is important to note in this regard that the cellular lipid metabolism is very complex and involves a large number of pathways and molecules with very little or no structural similarity at all. Further, changes in lipid metabolism are strikingly dependent on the time frame at which they occur. On the one hand, rapid lipid turnover and production of lipid mediators occurs immediately upon stimulus recognition. Cells achieve this by activating a limited set of pre-existing enzymes, and by reshaping their lipid pools to trigger an optimal response. On the other hand, prolonged exposure to stimuli leads to lipid reprogramming that involves not only pre-existing enzymes but also transcriptionally-regulated events that culminate in the expression of certain protein effectors [13,16–19]. In the following sections we discuss some relevant examples of processes occurring in both time scales which involve the turnover of discrete lipid classes primarily under inflammatory conditions.

2. Phospholipid compartmentalization

Alterations in the lipid metabolism represent one of the acute responses of cells to receptor stimulation. In innate immune cells, a common feature of ligand recognition is the spatial organization of PRRs and their downstream effectors, which involves electrostatic interactions with membrane lipids that are critical for their localization and functions. Lipid remodeling takes place at the very first level of pattern recognition. This metabolic rearrangement ensures the appropriate cellular response to the pathogens and their ligand components [20]. A key attribute that determines how, when, and to what extent lipid remodeling occurs is the specific localization of the lipids within the cell. A number of studies have shown that, compared to membrane models, phospholipid diffusion processes across the cell membrane are reduced because the cell membrane is compartmentalized [21]. It has been suggested that the confinement of phospholipids depends on transmembrane proteins anchored to the actin membrane skeleton network that, acting as picket rows, temporarily confine phospholipids. These phospholipids would be necessary to localize the intracellular signals to the point where the extracellular signal was received [21].

Substrate specificities for lipid-metabolizing enzymes, as obtained from *in vitro* assays, may not necessarily reflect the situation in live cells. The compartmentalization of substrates and products and the presence of competing enzymes may dramatically modify the specificities reported. Among the phospholipase A_2 (PLA_2) enzymes, the group VIA calcium-independent phospholipase A_2 ($iPLA_2\beta$) provides a good example of this. Most membrane phospholipids contain two fatty acids esterified at the *sn*-1 and *sn*-2 positions of the glycerol backbone (1,2-diacylglycerophospholipids). However there are phospholipids that contain an ether bond at the sn-1 positions instead of an ester bond (1-alkyl-2-acyl-glycerophospholipids), and there are some that also contain a cis-double bond conjugated with the ether oxygen (1-alkenyl-2-acyl-glycerophospholipids) (Fig. 1). The latter are called plasmalogens. A recent study by Hayashi *et al.* [22] demonstrated that $iPLA_2\beta$ shows no preference for the *sn*-1 linkage in the phospholipid substrate (i.e. ester, alkyl or alkenyl); yet, in cells the enzyme preferentially hydrolyzes phospholipid substrates which contain a palmitoyl moiety esterified at the *sn*-1 position [23,24]. This clearly suggests that, under physiologically relevant settings, the $iPLA_2\beta$ works on membrane compartments enriched in *sn*-1-palmitoyl-containing phospholipids, a feature that cannot be ascertained in an *in vitro* assay system. Further support to this view was provided by the studies of Chamulitrat and co-workers utilizing $iPLA_2\beta$ knockout mice in models of obesity and non-alcoholic fatty liver disease and steatohepatitis [25–28]. In these studies, $iPLA_2\beta$ was found to be associated with a decreased hydrolysis of sn-1-palmitoyl-containing PC and PE [25–28]. Interestingly, in these studies some preference of the enzyme for sn-1-stearoyl phospholipids was appreciated as well, suggesting a more widespread role for $iPLA_2\beta$ in the hydrolysis of phospholipids with saturated fatty acyl chains at the *sn-1* position [25–28].

In the aforementioned study of Hayashi *et al.* [22] it was also demonstrated that group IVA cytosolic Ca^{2+}-dependent $PLA_2\alpha$ ($cPLA_2\alpha$) shows selectivity for plasmalogen substrates *in vitro*. However, mass spectrometry-based lipidomic analyses of $cPLA_2\alpha$ substrates in activated macrophages did not reveal striking differences between the hydrolysis of plasmalogens and diacylphospholipids by $cPLA_2\alpha$ [23]. Also, it has been shown that the $cPLA_2\alpha$-dependent AA mobilization of macrophage cell lines is independent of their cellular plasmalogen content [29,30]. Thus the substrate specificity of $cPLA_2\alpha$ may also be primarily dictated by the phospholipid composition of the subcellular compartment where it acts.

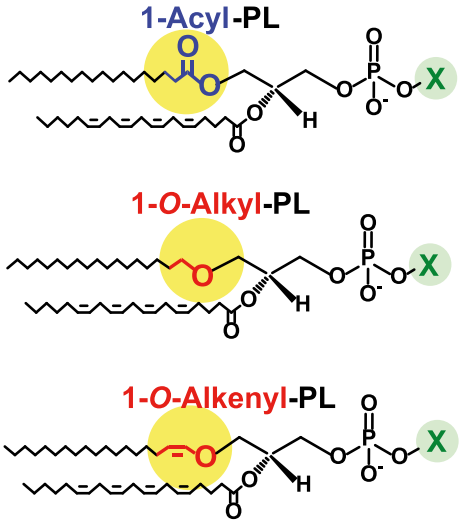

Fig. 1. Diversity of sn-1 bonds in membrane glycerophospholipids. Phospholipids containing an ester bond at the sn-1 position are the most common (blue, top). However, phospholipids containing an ether bond (1-O-Alkyl; red, middle) or vinyl ether bond (1-O-Alkenyl; red, bottom) bond are also found at significant levels in many cell types. 1-Alkenyl glycerophospholipids are called plasmalogens.

Another remarkable example of phospholipid compartmentalization was provided by studies carried out in neurons by Kuge *et al.* [31]. The authors showed that 1-oleoyl-2-palmitoyl-*sn*-glycero-3-phosphocholine is concentrated at the protrusion tips of neuronal culture cells and the presynaptic area of neuronal synapses of the mouse brain. This location is highly specific for this particular species, which undergoes hydrolysis at the *sn*-1 linkage by phospholipase A_1, and is considered a mechanism for protein confinement at the synapse [31]. In immune cells, the role of particular phospholipid species in TLR-mediated responses has been suggested from studies where exogenous lipids were added to the cells. One example is the phosphatidylserine species PS(38:4), which reduced the bacterial lipopolysaccharide-induced release of CXCL8 and CXCL10 in activated THP-1 cells [32]. These effects were later confirmed by the work of Köberlin *et al.* [33] investigating how the membrane lipid composition affects receptor-mediated signaling processes. In this study, the diverse steps of TLR signaling were compared with lipidomic network changes, and a negative correlation was found between the content of endogenous PS species associated with the plasma membrane and the presence of TLR4 at the plasma membrane level and inflammatory cytokine release [33].

Polyunsaturated phospholipid species have also been reported to be important for the induction of plasma membrane bending and fission. This is due to the capacity of these species to adapt their conformation to membrane curvature, thus reducing the energetic cost of these processes [34]. By facilitating endocytic events driven by endophilin and dynamin, polyunsaturated phospholipids participate in the endocytosis processes that occur during TLR activation or phagocytosis [34].

The turnover of inositol phospholipids at the plasma membrane of activated cells, in particular the species 1-stearoyl-2-arachidonoyl-sn-glycero-3-phosphoinositol (PI(18:0/20:4)), constitutes another meaningful instance of phospholipid compartmentalization. The role of inositol phospholipids in the signaling events following receptor activation during a phagocytic process has been extensively characterized [35]. PI(18:0/20:4) is the most abundant PI species in cells [36–38]. It is synthesized in the ER/trans Golgi and then transported to the plasma membrane, where phosphorylation of the inositol ring at the 4 and 5 positions occurs. After the release of inositol 1,4,5-trisphosphate by receptor-activated phospholipase C enzymes, the diacylglycerol species DG(18:0/20:4) is transported back to the ER/trans Golgi [39], and phosphorylated to form the phosphatidic acid molecular species that is subsequently converted to CDP-DG(18:0/20:4) and then to PI, thus completing the arachidonate PI cell cycle. The presence of AA in this species is the result of the intersection of this pathway with the Lands pathway of phospholipid remodeling, residing also at the ER [40,41] (Fig. 2; see Section 3). As noted above, extensive lipidomic studies demonstrated that the subcellular localization of PI(18:0/20:4) is not uniform, being divided mostly between the ER and the plasma membrane [42]. The very high level of this species at the plasma membrane is likely due to it being necessary for the resynthesis of phosphatidylinositol-4,5-bisphosphate, which is hydrolyzed at this location following receptor occupancy. In this context, the parallel mobilization of AA, not only from PI but also from other phospholipid classes, constitutes another interesting case of phospholipid compartmentalization involving the translocation of multiple effectors. The disparate distribution of AA among different cellular pools [43] and the translocation responses of the enzymes that metabolize AA [44–48] are being increasingly recognized as two key limiting factors for eicosanoid biosynthesis. These aspects are further commented on in Section 3.

3. Phospholipid remodeling via fatty acid transacylation reactions. Role of plasmalogens

A major lipid metabolic event that follows from receptor occupancy in many cell types is the loss of polyunsaturated fatty acids (PUFA) from membrane glycerophospholipids as a consequence of the activation of cellular PLA_2 enzymes [49,50]. Free PUFAs released in this way can be

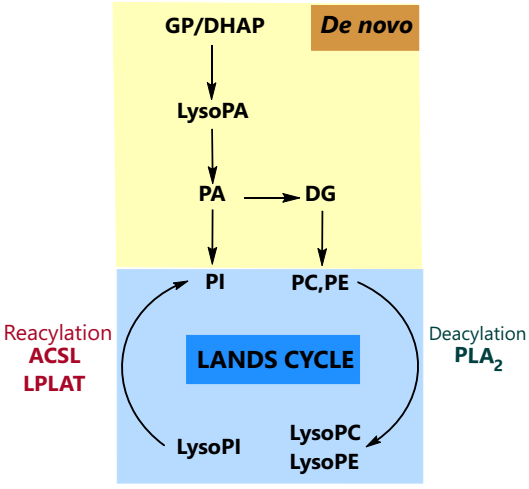

Fig. 2. De novo biosynthesis of phospholipids and the Lands pathway. Briefly, by the sequential action of CoA-dependent acyltransferases, lysophosphatidic acid (lysoPA) and phosphatidic acid (PA) are formed from glycerol phosphate (GP) or dihydroxyacetone phosphate (DHAP). PA is the precursor of phosphatidylinositol (PI). PC and PE are synthesized from diacylglycerol (DAG), which comes from the dephosphorylation of PA. The *de novo* pathway typically results in glycerophospholipids primarily containing saturated or monounsaturated fatty acyl chains. Major changes in phospholipid fatty acid composition occur via a subsequent deacylation/reacylation cycle known as the Lands cycle (blue box). Briefly, a PLA_2 removes the acyl chain present at the sn-2 position, generating a 2-lysophospholipid. The sequential action of long chain acyl-CoA synthetase (ACSL) and CoA-dependent acyl transferases (LPLAT) leads to the incorporation of another fatty acid, thus forming a phospholipid with a different acyl chain composition. The Lands pathway represents the major route for the incorporation of PUFAs into glycerophospholipids.

oxygenated to form a wide variety of metabolites with pro- or anti-inflammatory activity, namely the AA-derived eicosanoids and the *n*-3 PUFA-derived specialized pro-resolving mediators, respectively [11,51]. In addition to this 'classic' metabolic fate, unmetabolized free PUFAs can also interact with a number of receptors [52,53], or undergo uncontrolled nitration [54], sulfation [55] and oxidation [56,57], thereby generating a wide array of biologically active compounds. Furthermore, the other products of the PLA_2 reaction, the 2-lysophospholipids, can be released and act as secondary paracrine mediators [58].

Among the many PLA_2s expressed in cells and tissues, $cPLA_2\alpha$ has emerged as the fundamental enzyme regulating PUFA release during cell activation [59–62]. The mechanism of activation of $cPLA_2\alpha$ has been shown to involve the concerted action of mitogen-activated protein kinase-driven phosphorylation cascades and transient elevations of the intracellular Ca^{2+} concentration [59–62]. In addition, the bioactive lipids phosphatidylinositol-4,5-bisphosphate and ceramide-1-phosphate regulate the subcellular localization and activation of $cPLA_2\alpha$ [63,64].

Most PUFAs, including AA, preferentially localize at the *sn*-2 position of membrane glycerophospholipids, and this asymmetric PUFA distribution constitutes a key regulatory aspect of membrane phospholipid homeostasis [65]. Once a PUFA is obtained from the diet or synthesized from its essential precursors, inflammatory cells use select pathways to distribute the fatty acids into specific glycerolipid pools. Unless available at high micromolar levels, PUFAs, in particular AA, are not generally incorporated into cellular phospholipids via the *de novo* biosynthetic pathway (i.e acylation of glycerol 3-phosphate or acyl-glycero-3-phosphate to form phosphatidic acid). Instead AA does it so at a later stage, via the so-called Lands pathway, which involves the direct acylation of pre-existing lysophospholipids, particularly lysoPC and lysoPI, with the fatty acid [66] (Fig. 2). Given the preference of PUFAs for the *sn*-2 position of phospholipids, the lysophospholipid acceptors required for fatty acid incorporation within the Lands cycle are

those produced by PLA_2s [67,68]. On the other hand, two families of lysophospholipid acyltransferase enzymes have been recognized, namely the membrane bound O-acyltransferase (MBOAT) family and the 1-acyl-glycerol-3-phosphate O-acyltransferase (AGPAT) family [69]. MBOAT7 (also known as lysoPI acyl transferase, LPIAT) in the ER/trans Golgi specifically binds arachidonoyl-CoA ester to lysoPI(18:0) to form the abundant molecular species PI(18:0/20:4). MBOAT5 (also known as lysoPC acyl transferase 3, LPCAT3) is responsible for the incorporation of AA moieties into various species of PC and PE [69].

For the asymmetrical distribution of PUFAs in phospholipids to be fully achieved, a further remodeling step is required, whereby the phospholipid-bound fatty acid is directly transferred to other phospholipids without the formation of an acyl-CoA intermediate [43,70,71]. This reaction is catalyzed by CoA-independent transacylase (CoA-IT), which directly transfers the fatty acyl moiety of a phospholipid donor (usually diacyl-PC) to a lysophospholipid acceptor (usually diacyl-PE and alkenyl-PE) [43,70,71] (Fig. 3). Thus, globally, remodeling of AA and other PUFAs is governed by acyl-CoA synthetases, which activate the fatty acid through thioesterification with CoA, CoA-dependent acyltransferases, which bind the fatty acid to a lysophospholipid acceptor, and the CoA-independent transacylase (CoA-IT), which moves the AA between phospholipid classes.

Phospholipid fatty acid remodeling is necessary for cells of the innate immune system to distribute AA and other PUFA acid within the appropriate cellular pools for its subsequent mobilization by PLA_2 enzymes. This is a key aspect in eicosanoid regulation because the nature and amount of eicosanoids produced under activation conditions may ultimately depend on compartmentalization, i.e. the composition and subcellular localization of the phospholipid pool where the AA-hydrolyzing PLA_2 acts [44,49]. In innate immune cells, ether

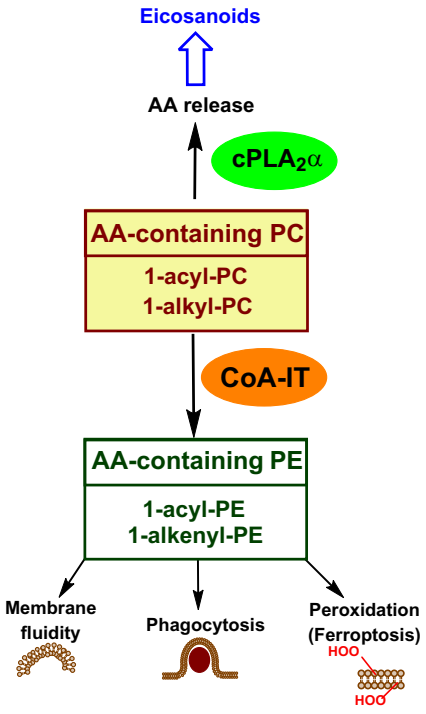

Fig. 3. Dual role of AA-containing PC in lipid signaling. During cellular stimulation, AA-containing PC is acted upon by $cPLA_2\alpha$, and this reaction represents the major source of free AA for the synthesis of select eicosanoids. In addition, the AA moiety of AA-containing PC (mostly the 1-acyl-2-AA-PC species) can be transferred directly to lysoPE (both acyl- and alkenyl-PE species) by CoA-IT to generate 1-acyl-2-AA-PE and 1-alkenyl-2-AA-PE. The CoA-IT reaction controls the cellular levels of AA-containing PE, which serves important roles, such as the control of membrane fluidity, modulation of phagocytosis, and the initiation of ferroptosis when the AA chain becomes oxidized.

phospholipids, particularly the ethanolamine plasmalogens, are strikingly enriched with AA. This appears to be a consequence of the strong preference of CoA-IT for ethanolamine lysoplasmalogens as acceptors in the AA transacylation reaction [43,72]. Yamashita and co-workers first proposed that CoA-independent transacylation reactions leading to AA remodeling are mediated by (an) enzyme(s) of the PLA_2 family and thus could represent an undescribed activity of an otherwise known enzyme [72–76]. Based on the biochemical properties of the transacylation reaction, the group IVC cytosolic phospholipase $A_2\gamma$ ($cPLA_2\gamma$) was suggested as a possible candidate. This proposal obtained experimental support by later work of Lebrero *et al.* [29] showing that cells deficient in $cPLA_2\gamma$ transfer AA from PC to PE at a significantly lower rate than cells containing normal levels of the enzyme. Importantly however, the latter study also noted that $cPLA_2\gamma$ is likely not the only enzyme acting as a CoA-IT in cells [29]. Clearly, these additional effectors acting as CoA-IT in activated cells will need to be identified and characterized before a full understanding of the regulatory features of phospholipid AA remodeling is obtained.

Intriguingly, $cPLA_2\gamma$ has been shown to contribute to lipid droplet accumulation in hepatocytes [77,78], and there is a sizeable body of literature implicating diverse PLA_2 enzymes in lipid droplet structure and dynamics [79–81]. Whether the CoA-IT transacylase activity of $cPLA_2\gamma$ plays a role in these processes is currently unknown but, as discussed by Su and co-workers [78], the possibility exists that transacylation of AA moieties from PC stores to ethanolamine plasmalogens may entail the location of AA moieties into PL pools more accessible to enzymes, thus favoring intracellular signaling leading to lipid droplet formation. It is also possible that the enrichment of plasmalogens with AA within the lipid droplet improves biophysical properties –i.e. charge, fluidity– that support the optimal assembly of the organelle.

While the enrichment of ethanolamine plasmalogens with AA clearly suggests a central role for these species in AA homeostasis, their function still remains obscure. In fact, receptor stimulation of AA mobilization in plasmalogen-deficient cells is similar to that of normal cells, suggesting that plasmalogens are not essential for the cells to effect a full AA release response [30,82]. Moreover, no differences have been found either in the rate of CoA-IT-dependent phospholipid AA remodeling between plasmalogen-deficient and otherwise normal cells, suggesting that cellular plasmalogen status also has no influence on phospholipid AA remodeling [29].

Importantly, recent data have suggested that the CoA-IT-mediated remodeling reaction may represent an important point of control of the amount of AA available for eicosanoid biosynthesis. This is based on the dual role that AA-containing PC species appear to serve during cellular activation. On the one hand, AA-containing PC is the major donor of the fatty acid moieties that are used in the CoA-IT-catalyzed reaction. On the other hand, the synthesis of select eicosanoids by activated innate immune cells appears to be specifically linked to the mobilization of free AA from PC [23,84–89] (Fig. 3). Thus, competition between these two pathways for utilization of AA-containing PC may determine the amount of free AA available to feed the cyclooxygenases and/or lipoxygenases under activation conditions, this representing an effective means to regulate the overall eicosanoid response. In support of this view, studies with activated macrophages recently unveiled an inverse relationship between the extent of CoA-IT-mediated phospholipid AA remodeling from PC to PE and the amount of eicosanoids produced in response to receptor stimulation [90]. Similarly, the well described enhancing effect of bacterial lipopolysaccharide on macrophage AA release and eicosanoid production [91] was also found to correlate with reduced usage of AA for CoA-IT-mediated remodeling [30].

Another striking outcome of the CoA-IT-driven AA remodeling is that the transfer of AA moieties from AA-containing PC to PE prevents a decline in the cellular amount of the latter during cellular stimulation. The net result is that AA levels in PE species change little as a consequence of cell activation, at the expense of stronger decreases in PC [23,36,83,87,88]. This, together with the finding that AA-containing PE

does not appreciably contribute to acute prostaglandin and leukotriene production in activated inflammatory cells [23,84–89], raises the intriguing possibility that the enrichment of ethanolamine plasmalogens with AA may not be necessarily related to regulatory aspects of AA homeostasis and eicosanoid metabolism. Instead, it could be related to biophysical effects and interactions of AA-containing PE molecules with other membrane components to sustain different biological responses [92,93]. Enrichment of newly formed plasmalogens with AA may provide a counteracting force for finer regulation of changes of the biophysical properties of the membrane. In this regard, recent studies have demonstrated that the cellular ethanolamine plasmalogen pool in macrophages determines characteristics of the plasma membrane such as fluidity and the formation of microdomains that are essential for efficient signal transduction leading to optimal phagocytosis [37,94]. Other studies have demonstrated a decrease of plasmalogen levels in sepsis in rodents and SARS-CoV-2 infection in humans, suggesting a protective role for these phospholipids during oxidative stress associated with infectious diseases [95]. Furthermore, in accordance with the growing data regarding the phenomenon of ferroptosis and the pivotal role that oxidized PE plays in this process [96,97] (see Section 5), it is certainly possible that the presence of high levels of AA and other easily oxidized PUFAs in ethanolamine plasmalogens [49] is related to the ability of cells to mount a proper and efficient ferroptotic response.

The CoA-IT-mediated phospholipid remodeling pathway is not confined to 'traditional' immune cells, but has also been recognized in other cell types, most notably platelets. It is in these cells that some of the first indications on the importance of this route to shaping the distribution of AA between phospholipids were made [98,99]. While having primary roles as mediators of hemostasis and thrombin generation, platelets also serve multiple functions related to inflammation and immunity. These cellular fragments express and secrete several pro- and anti-inflammatory molecules that participate in immune functions, such as the expression of Toll-like receptors or the secretion of many immunomodulatory cytokines and chemokines [100].

In addition to AA and related PUFAs, other phospholipid-bound fatty acids also undergo remodeling. This process may substantially modify the distribution of such fatty acids among the various cellular phospholipid molecular species, with potentially important pathophysiological consequences. This is the case of palmitoleic acid (16:1*n*-7) and its positional isomer hypogeic acid (16:1*n*-9). These two fatty acids exhibit marked anti-inflammatory activity and are becoming increasingly considered as metabolic markers with key biological functions in health and disease [101–105]. A striking feature of the distribution of palmitoleic acid and hypogeic acid in macrophages is that more than 80% of the cellular content of both fatty acids is present in a single phospholipid molecular species, namely 1-palmitoyl-2-palmitoleoyl/hypogeoyl-*sn*-glycero-3-phosphocholine, PC(16:0/16:1) [105,106]. Activation of the cells by pro-inflammatory stimuli such as bacterial lipopolysaccharide or yeast-derived zymosan results in the two fatty acids being transferred from PC(16:0/16:1) to the minor species 1-stearoyl-2-palmitoleoyl/hypogeoyl-*sn*-glycero-3-phosphoinositol, PI (18:0/16:1). It appears that this remodeling reaction involves the liberation of palmitoleic acid and hypogeic acid from PC by iPLA$_2\beta$ [106], its coupling to coenzyme A and subsequent reaction with the abundant lysoPI generated in monocytes/macrophages as a consequence of cell activation [23,107,108]. By modifying the distribution of hexadecenoic fatty acids among the various cellular species, this remodeling reaction may give rise to novel phospholipid signatures that identify specific activation states. More importantly, the significant increase of a particular PI species, PI(18:0/16:1), may endow the cells with novel or improved functions. Indeed, PI(18:0/16:1) has previously been suggested to mediate the proliferative response of fibroblasts to growth factors [109].

4. Oxidized phospholipids

Circulating blood cells (neutrophils, platelets, eosinophils) and resident murine peritoneal macrophages generate enzymatically oxidized phospholipids (eoxPL) in a controlled manner as part of the innate immune response [110–115]. Canonical eoxPL formation comprises the following steps: (i) PL hydrolysis by PLA$_2$s to release a fatty acid, (ii) formation of the oxidized fatty acid via cyclooxygenase (COX) or lipoxygenase (LOX), and (iii) re-esterification of the oxylipin to a lysophospholipid to form the eoxPL by the sequential action of fatty acyl-CoA synthetase and CoA-dependent acyl transferases [110–115]. It is important to note that COX and LOX can also oxygenate the fatty acid without it being in free form but still bound to the phospholipid, thus generating an eoxPL in a single step. The pathophysiological relevance and contribution of this alternative pathway of eoxPL formation may depend on cell type and stimulation conditions [116–118].

Human platelets can rapidly form >100 unique eoxPL species through 12-LOX and/or COX-1 after thrombin activation [119]. The most abundant are PEs, although PC forms are also abundant, and are produced preferentially with 12-HETE (either as plasmalogens or diacyl species). HETE-PI forms are also produced although to a lesser extent [120]. 14-Hydroxydocosahexaenoic acid (HDOHE)-PEs are also detected in platelets, which arise from DHA oxidation by 12-LOX [110]. Low amounts of eoxPL derived from adrenic acid (22:4*n*-6), docosapentaenoic acid (22:5*n*-3), and dihomo-γ-linolenic acid (20:3*n*-6) are also formed, as well as rarer oxidized AA species containing two or more oxygen atoms [119]. Epoxyeicosatetraenoic acids (EET), generated by the cytochrome P450 family of enzymes [121,122], may also be found esterified in phospholipids. EET-PLs alter membrane microdomain properties or may act as a releasable pool of oxylipins [121].

The very rapid formation of eoxPLs after cell stimulation suggests that the synthetic enzymes are localized at proximal sites and work cooperatively [115]. A key difference between eoxPLs and their eicosanoid precursors is that the former reside preferentially within membranes. For example, HETE-PLs mainly exert their effects through low-affinity interactions with proteins and/or altering membrane electronegativity and structurally forming what is called the whisker model [123]. Interestingly, whereas 5-LOX and 12-LOX generate HETE-PEs through fatty acid recycling in human innate immune cells [112], when direct PL oxidation occurs, it is mediated by 15-LOX in humans and its ortholog 12/15-LOX in mice, suggesting that compartmentalization of enzymes plays an important role in the synthesis of eoxPL and in their cellular functions [124,125].

The production of reactive oxygen species (ROS) by different types of cells constitutes a key defensive response in innate immunity, but also leads to the oxidation of biomolecules in a non-enzymatic manner, *e.g.* under oxidative stress or inflammatory conditions. Double bounds of polyunsaturated fatty acids esterified in PL are a frequent target for this kind of reactions, leading to the formation of non-enzymatically oxidized phospholipids (oxPLs) [116]. It is now well established that the formation of oxPLs is not just a side-effect or consequence of inflammatory conditions or oxidative stress, but that oxPLs elicit biological responses on their own. Thus they actively contribute to the inflammatory process [126,127] even in the absence of infection [128,129].

oxPLs interact with multiple PRRs, which may help to explain their strong pro- or anti-inflammatory character [130–134]. Some relevant species are 1-palmitoyl-2-(5-oxovaleroyl)-*sn*-glycero-3-phosphocholine (POVPC), and 1-palmitoyl-2-glutaroyl-*sn*-glycero-3-phosphocholine (PGPC). These two oxPLs can inhibit bacterial phagocytosis in alveolar macrophages, hence impairing bacterial clearance in vivo [135]. High concentrations of oxidized 1-palmitoyl-2-arachidonoyl-*sn*-glycero-3-phosphocholine (oxPAPC) mixtures trigger the intracellular inflammasome pathway [136]. In contrast, 1-palmitoyl-2-(5,6-epoxy isoprostane E$_2$)-*sn*-glycero-3-phosphocholine (PEICP) and 1-palmitoyl-2-(5,6-epoxy isoprostane A$_2$)-*sn*-glycero-3-phosphocholine (PECPC) blunt the

proinflammatory cytokine responses induced via multiple TLRs in dendritic cells and macrophages [137–139]. Freigang *et al.* [140] highlighted the role of the non-enzymatic cyclopentenone-containing oxPLs as class of potent anti-inflammatory lipid mediators with therapeutic potential. Most, if not all, of the anti-inflammatory activities of cyclopentenone oxPLs have been shown to be mediated via Nrf2 (transcriptional regulator of the antioxidant response, NF-E2-related factor 2) [140].

Recently, a novel defense mechanism has been identified in activated neutrophils, the so-called NETosis, a type of cell death that is associated with the extracellular release of histone and protease-coated chromosomal DNA, forming web-like structures [141]. These structures are named neutrophil extracellular traps (NETs), and play critical roles in the efficient elimination of bacteria by helping immobilize them. NETs are generated in response to a variety of stimuli that produce ROS in an NADPH oxidase-dependent manner [142–144]. Recent work by Yotsumoto *et al.* [145] showed that NET formation is promoted by the non-enzymatic oxidation of ether-containing phospholipids. The release of these oxidized phospholipids induced the sequential activation of NET formation and NETosis in neighboring neutrophils. This study also showed that sulfasalazine, a compound used to ameliorate bowel inflammation or rheumatoid arthritis, promoted NET formation by isolated neutrophils by mechanisms related with the increased generation of oxidized ether-containing phospholipids, such as PE(O-18:1/15-HETE) and PC(O-16:0/13-HODE). These findings, together with recent studies on ferroptosis, discussed in Section 5, shed light into the role of oxidized phospholipids as executioners or modulators of specific types of cell death. NETosis does not share the common mechanisms of ferroptosis nor does it require the enzymatic activity of 12/15-LOX, which is involved in the induction of ferroptosis in glutation peroxidase 4 (GPX4)-deficient cells [146,147]. Thus, NETosis is essentially different from ferroptosis, although both types of cell death involve lipid oxidation.

In other studies, Shimanaka *et al.* [148] described a new class of lipid mediators that enhance mast cell activation and anaphylaxis, namely 17,18-epoxyeicosatetraenoic acid (17,18-EpETE) and 19,20-epoxydocosapentaenoic acid (19,20-EpDPE). These mediators were released from their esterified precursors, that is, *n*-3 epoxide–containing phospholipids, by platelet activating factor acetylhydrolase-2 (also known as group VIIB phospholipase A_2). It was not clarified, however, whether the *n*-3 fatty acids esterified in phospholipids were directly oxygenated or the n-3 fatty acids were first oxygenated in the form of free fatty acids and then esterified into phospholipids. Having bioactive oxygenated fatty acids in the form of their esterified precursors ensures stable reservoirs of otherwise fragile *n*-3 epoxides to hydrolases to support certain cell functions. In fact, in a model of IgE-mediated mast cell activation, it was found that both 17,18-EpETE and 19,20-EpDPE blunted FcεRI signaling by inhibiting PPARγ [148].

In spite of all the recent advances, the mechanisms underlying the immunomodulatory properties of oxPLs and eoxPLs still remain largely unexplored. Depending on cell type, the site of generation, and the nature and amount of the individual phospholipid species, the mechanisms and actions may substantially vary [114,139,149–152]. What is gaining strong support however, is the central role that the phospholipase $iPLA_2\beta$ plays in the clearance of oxidized phospholipids under a wide variety of conditions. This aspect is discussed in detail in Section 5.

5. Ferroptosis

Ferroptosis is a regulated form of necrosis that is implicated in numerous processes including cell death during tissue turnover, cancer cell death, and aggravation of tissue injury [153,154]. Ferroptosis involves the rapid and massive generation of oxidized PLs in an iron-dependent manner. It has been extensively described in cellular settings where antioxidant mechanisms based on glutation, such as GPX4, are reduced [125,146,155]. The presence of PLs with long polyunsaturated *n*-6 fatty acids in cellular membranes is a prerequisite for the formation of oxidized PLs during ferroptosis. Recent redox lipidomic analyses have revealed that, out of all classes of PLs, oxidized arachidonoyl (AA)- or adrenoyl (AdA)-containing PE species act as the main executioners of ferroptotic death, and they are present in ER-associated compartments [125,156]. AdA is the 2-carbon elongation product of AA. The two fatty acids share many biochemical commonalities, but also striking differences. Both fatty acids are distributed similarly among cellular phospholipid species in immunoinflammatory cells, but they do not compete with each other, *i.e.* incorporation of AA into phospholipids does not displace AdA, nor AdA incorporation displaces AA [157,158]. While both fatty acids are mobilized at significant amounts during innate immune cell activation, the effectors involved vary; AA release proceeds almost exclusively via $cPLA_2\alpha$, but AdA mobilization also involves $iPLA_2\beta$ acting primarily on PC [158]. Of note, AdA mobilization has been linked to the execution of anti-inflammatory responses by innate immune cells [159]. As previously discussed in Section 2, other fatty acid products of $iPLA_2\beta$-cleavage of membrane phospholipids, namely the hexadecenoic fatty acids palmitoleic acid and hypogeic acid, also display strong anti-inflammatory activity. Furthermore, previous work had also identified $iPLA_2\beta$ as the major mediator of docosahexaenoic acid (22:6*n*-3) metabolism and signaling in brain [160,161]. The anti-inflammatory effects of docosahexaenoic acid and its oxygenated metabolites are well documented [11]. Together, these data raise the intriguing suggestion that an important role for $iPLA_2\beta$ in pathophysiology is to function as a master regulator of lipid signaling pathways that lead to the generation of protective anti-inflammatory responses (Fig. 4). The central role that this phospholipase also plays in clearing oxidized membrane phospholipids (see below), is in full agreement with this view.

It should be indicated, however, that pro-inflammatory roles for $iPLA_2\beta$ have been described as well. These include studies showing that $iPLA_2\beta$-deficient mice exhibit protection against steatosis, inflammation, fibrosis, and hepatocellular carcinoma [162,163]; and the failure of $iPLA_2\beta$-deficient macrophages to kill *Trypanosoma cruzi* [164] and to upregulate markers of M1 polarization [164–166]. It was anticipated some 20 years ago [167,168], and it is now becoming evident, that $iPLA_2\beta$ is a multifaceted enzyme which, depending on conditions, may exert multiple functions in different cells and tissues.

The chemical nature of AA and AdA as long-chain *n*-6 fatty acids and the necessity for their oxidized forms to be esterified into phospholipids

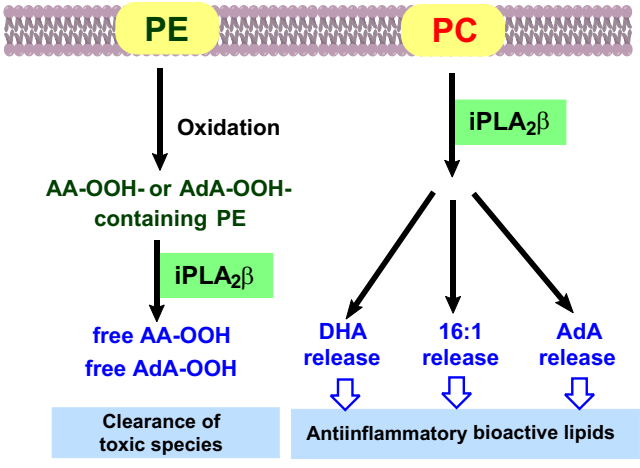

Fig. 4. New insights into the pathophysiological role of $iPLA_2\beta$-regulated pathways. $iPLA_2\beta$ regulates a number of lipid signaling pathways leading to protective anti-inflammatory actions. These include clearance of oxidized PE species during ferroptosis, and mobilization of docosahexaenoic acid (DHA, 22:6n-3), palmitoleic and hypogeic acids (hexadecenoic fatty acids, 16:1) and adrenic acid (AdA) from PC pools upon macrophage stimulation.

to participate in ferroptosis explains the relevance of the enzymes of the Lands cycle in regulating ferroptotic lipid signaling, including in addition to cPLA$_2$α and iPLA$_2$β, the acyl-CoA synthetase forms -1, -3, and -4, and the acyl transferase LPCAT3 [155,169]. LOX, but not COX or cytochrome P450, is also involved in generating peroxidation signals [125,156] (Fig. 5).

In studies dealing with phagocytosis of ferroptotic leukemic cell lines, Luo *et al.* [170] found that the process occurred simultaneously with the accumulation of oxidized PLs, especially PE hydroperoxides. Extensive phospholipidomic analyses of the plasma membrane of ferroptotic cells led to the identification of the species 1-stearoyl-2-15-HPETE-sn-glycero-3-phosphoethanolamine (SAPE-OOH) as the primary signal in ferroptotic cells that promoted phagocytic clearance, and TLR2 as the receptor responsible for directly recognizing SAPE-OOH [170].

An intriguing question in ferroptotic lipid signaling is why the process preferentially involves the ethanolamine phospholipid class over all other classes. Using live cell imaging, it was demonstrated that hydroperoxide-containing PE species (PE-OOH) predominantly accumulate in the extra-mitochondrial ER-associated compartments, in the vicinity of the LOX enzymes responsible for their synthesis [125,171]. Model biochemical experiments and computer simulations indicated that nonbilayer (possibly hexagonal) arrangements of AA- and AdA-PE, in contrast to the highly ordered bilayer organization of AA-PC, facilitate the availability of these phospholipid substrates for binding and enzymatic attack by 15-LOX. Regarding the plasma membrane, it is also possible that the prevalence of PE in the inner leaflet [172,173] contributes to the preferential oxidation by LOX, whereas confinement of PC to the outer membrane monolayer is not conducive to its interactions with the intracellular oxidizing machinery.

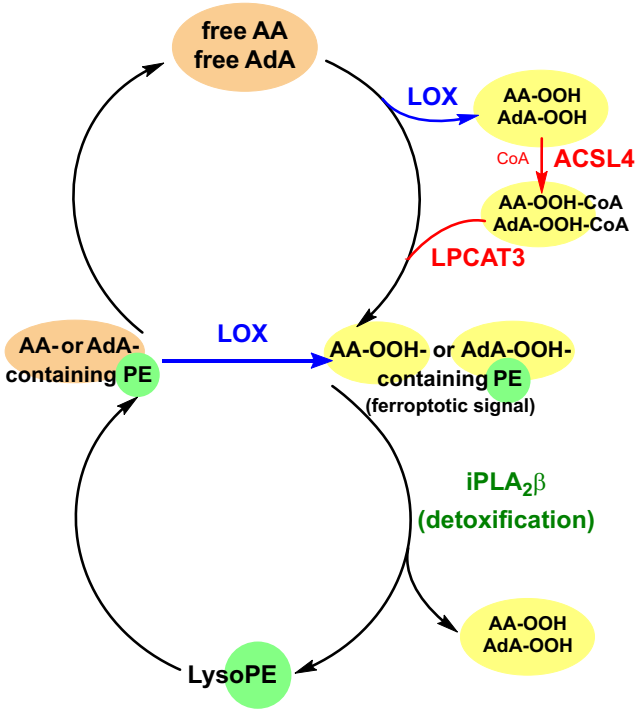

Fig. 5. Generation of oxidized PE during ferroptosis. Lipoxygenase (LOX) oxidizes free AA and AdA (AA-OOH and AdA-OOH, respectively) and these oxidized fatty acids are incorporated into membrane PE by the concerted action of acyl-CoA synthetase and CoA-dependent acyl transferase (ACSL-4 and LPCAT3). Alternatively, AA- or AdA-containing PE species can be acted upon by LOX, directly generating oxidized PE species. Accumulation of oxidized PE constitutes a bona fide ferroptotic signal that is "cleaned up" from membranes by the action of iPLA$_2$β, which removes the oxidized fatty acid. The resulting lysoPE can then re-esterified with another fatty acid to form new PE.

The importance of oxidizedAA-containing PE to ferroptosis may suggest that the cells possess mechanisms to maintain the cellular levels of AA-containing PE at relatively stable levels to ensure an appropriate ferroptotic response when necessary. This should be so even under conditions of receptor activation, where large amounts of AA (and also AdA) are lost from membrane phospholipids. Interestingly, extensive lipidomic analyses have demonstrated that, when innate immune cells are activated by phagocytic stimuli, little AA is mobilized from PE, in contrast with the high amounts of fatty acid being liberated from PC and PI [23,36,83,87,88]. The AA liberated from PE is rapidly and effectively replenished by the action of the enzyme CoA-IT at the expense of AA-containing PC [43,70,72]. Thus it may be reasoned that AA-containing PE constitutes a relatively stable reservoir which is ready to be oxidized in critical moments to exert other functions than merely providing free AA substrate for eicosanoid synthesis.

In turn, removal of oxidized fatty acyl chains from membrane phospholipids by PLA$_2$s constitutes a major regulatory point for the control of ferroptosis. While cells express multiple PLA$_2$ enzymes potentially capable of removing oxidized fatty acids from membranes, iPLA$_2$β plays a significant role in this regard [59]. As such, this enzyme has been found to mediate the detoxification of peroxidized lipids and, consequently, the suppression of ferroptosis under a number of experimental conditions [174–176].

The involvement of iPLA$_2$β in the removal of oxidized fatty acyl chains was described well before the concept of ferroptosis came into place, as a special case of the originally proposed function of the enzyme in phospholipid fatty acid recycling [68,177,178]. Oxidative stress accelerates the iPLA$_2$β-catalyzed fatty acid release from membrane phospholipids, including mitochondrial cardiolipin, by mechanisms involving disturbance of the membrane structure, which in turn increases susceptibility/accessibility of the enzyme to its substrate [179–183]. Consistent with these early observations, a recent study demonstrated that ferroptosis in human trophoblasts, occurring after inhibition or depletion of either GPX4 or iPLA$_2$β, is accompanied by dramatic changes in the trophoblast plasma membrane, with macroblebbing and vesiculation [184]. Molecular modeling showed that the accumulation of peroxidized PE was directly associated with the structural changes observed [184].

iPLA$_2$β-mediated phospholipid hydrolysis during oxidant injury was also long known to be involved in the apoptotic process itself, and also in providing accessory attraction signals such as the production of lysoPC, which are necessary for the efficient elimination of dead cells and debris by the macrophages [185–190]. Thus a key concept that emerges from all these studies is the multiplicity of roles that iPLA$_2$β may play during apoptotic cell death. In addition to participating in apoptosis as indicated above, the enzyme may also assist in repairing oxidized mitochondrial membrane components (*e.g.* cardiolipin), thus preventing cytochrome *c release* [191].

Significant accumulations of peroxidized PE have been detected in mice with deficiency or function-perturbing mutations of iPLA$_2$β related to mitochondrial dysfunction [192,193]. It has also been shown that spontaneous preterm birth in humans is associated with injured placentas exhibiting high levels of peroxidized PE, consistent with placental ferroptosis. iPLA$_2$β-deficient mouse trophoblasts exhibit enhanced sensitivity to ferroptosis, consequently increasing placental damage, and risk of fetal demise [176]. Other studies have demonstrated that genetic abatement of iPLA$_2$β in SH-SY5Y neuronal cells, H109 fibroblasts and BeWo trophoblasts or fibroblasts from a patient with Parkinson Disease with a naturally occurring mutation in the *PNPLA9* gene (encoding for iPLA$_2$β) resulted in diminished hydrolytic activity toward 15-HPETE-PE [175]. This led to increased intracellular levels of 15-HPETE-PE and enhanced sensitivity to RSL3-induced ferroptosis, as compared to wild-type controls. Besides, the *Pnpla9*$^{R748W/R748W}$ mice exhibited progressive parkinsonian motor deficits along with 15-HPETE-PE accumulation [175]. Overall, these data have provided support for a pivotal role of

iPLA$_2$β in eliminating ferroptotic signals via clearance of oxidized phospholipids, and paralleling in this manner the GPX4-mediated defense mechanisms.

The tumor suppressor p53 is known to sensitize cancer cells to ferroptosis in a GPX4-independent manner by repressing the expression of SLC7A11, a component of the cystine/glutamate antiporter which also binds to 12-LOX and inhibits its lipid peroxide activity [194,195]. By increasing SLC7A11, cancer cells can protect themselves from p53-induced ferroptosis. It was recently shown that depletion of endogenous iPLA$_2$β sensitized tumor cells to ferroptosis, consequently enhancing p53-dependent tumor growth suppression. Both oxPE(18:0/22:4) and oxPC(18:0/20:4) levels were significantly induced upon 12-LOX overexpression in tumor cells [174]. As these elevated levels were effectively reduced upon co-expression of iPLA$_2$β, it was concluded that iPLA$_2$β can block ferroptosis by abrogating 12-LOX-induced lipid peroxidation [174]. Thus these results unveil an alternative route for p53-driven ferroptosis upon ROS-induced stress where iPLA$_2$β-mediated detoxification of peroxidized lipids acts as a critical and sufficient regulator of the process in a GPX4-independent manner.

Two recent studies have identified the flavoprotein FSP1 (ferroptosis suppressor protein 1, also known as apoptosis-inducing factor mitochondria-associated 2, AIFM2) as another important regulator of ferroptosis [196,197]. The antiferroptotic role of FSP1 was found to be independent of canonical ferroptosis regulators such as cellular glutathione levels, GPX4 activity, and oxidizable fatty acid content. Due to the well known NADH:ubiquinone oxidoreductase activity of AIF proteins, it was suggested that FSP1 mediates, in a NAD(P)H-dependent manner, the transference of reducing equivalents from CoQ10 or α-tocopherol into lipid bilayers to ameliorate the propagation of lipid peroxidation. Thus, FSP-1 is part of another alternate protective system that co-operates with glutathione and GPX to suppress phospholipid peroxidation and ferroptosis [196,197]. Interestingly, the anti-ferroptotic role of iPLA$_2$β is not only independent of GPX4, as indicated above [174], but also seems to be independent of FSP1, as p53-mediated ferroptosis in FSP1-null cells was suppressed by overexpression of iPLA$_2$β [174].

Recently, another protective mechanism against ferroptosis has been described, involving dihydroorotate dehydrogenease (DHODH). DHODH inhibits ferroptosis in the mitochondrial inner membrane, acting in parallel to mitochondrial GPX4 (but separately of cytosolic GPX4 or FSP1), through the reduction of ubiquinone to ubiquinol. DHODH and mitochondrial GPX4 thus constitute two major mechanisms for mitochondrial lipid detoxification [198]. Whether iPLA$_2$β is involved in this process remains to be investigated.

In addition to the actions of iPLA$_2$β, it is worth mentioning that another system for the detoxification of phospholipid hydroperoxides has been described in activated macrophages, namely the iNOS/NO• system [199]. This is an intriguing subject, as nitro-oxidative stress in inflammatory conditions yields nitro-fatty acids, including nitro-AA, which are novel anti-inflammatory signaling mediators [200–202]. It is also intriguing to speculate with the possibility that not only the cellular localization but also the chemical composition of the oxidized phospholipid, in particular the presence or absence of an ether bond at the *sn*-1 position, may have differential effects on the overall process of ferroptosis [203].

Cells express another member of the group VI family of lipases, namely the group VIB phospholipase A$_2$ – *PNPLA8*, commonly called Ca^{2+}-independent phospholipase A$_2$γ, iPLA$_2$γ – which may also be involved in the clearance of oxidized phospholipids. This enzyme has been found to participate in the removal of peroxidized cardiolipin from the mitochondrial membrane, thereby preserving membrane integrity [204]. Studies with iPLA$_2$γ knock-out mice revealed mitochondrial dysfunction and increased oxidative stress leading to lipid peroxidation and the loss of skeletal muscle structure and function [204]. Whether this enzyme – or other members of the group VI family – play also a role in ferroptosis is unknown at present.

Other enzymes of the Lands pathway of phospholipid fatty acid recycling have also been implicated in ferroptosis. This is the case of LPCAT3, an enzyme that reacylates lysoPC and lysoPE primarily with AA [205,206]. LPCAT3 was initially identified to play a role in ferroptosis induced by GPX4 inhibitors by using a haploid chronic myeloid leukemia cell line (KBM7 cell) where massive insertional mutagenesis was induced by gene-trap retroviral infection [169]. The result was later confirmed in mouse lung epithelial cells and embryonic fibroblasts silenced for the enzyme [175]. The decrease in LPCAT3 expression was accompanied by an increased resistance to ferroptosis and, as expected, elevated levels of 1-stearoyl-2-lyso-PE and 1-stearoyl-2-lyso-PC [175]. Importantly, the levels of pro-ferroptotic signals such as peroxidized PE or 1-stearoyl-2-HPETE-PC, that increased upon exposure to the GPX4 inhibitor RSL3, were significantly reduced in LPCAT3-deficient cells treated with RSL3 [175]. In keeping with these data, recent studies utilizing selective small-molecule inhibitors of LPCAT3 also demonstrated protection against ferroptosis induced by GPX4 inhibition [207]. Overall, these results support the involvement of LPCAT3 in ferroptosis by regulating the amount of esterified PUFAs whose oxidation generates ferroptotic signals. Interestingly, suppression of ACSL-4 (acyl-CoA synthetase-4) expression, the enzyme that acts upstream of LPCAT3 for the incorporation of polyunsaturated fatty acids into phospholipids via the Lands cycle, has also been found to blunt ferroptosis induced by GPX4 inhibition [138].

6. Concluding remarks

One of the key features of the initiation of the innate immune response is the reorganization of lipid metabolic routes, aimed to ensure the production of bioactive compounds and the reprogramming of energetic pathways that are necessary to support the process. Many bioactive lipids promote inflammation, acting in most cases as paracrine mediators, and helping as well in the initiation of the adaptive response. The cells effectively accomplish these tasks by strictly controlling the lipid metabolic routes leading to the production of functionally active lipids. One example is the tight cellular control of the level and composition of phospholipid molecular species, which is subjected to multiple remodeling reactions. This ensures multiple goals, e.g. the sustained availability of phospholipids enriched in polyunsaturated fatty acids for efficient eicosanoid/docosanoid synthesis; the maintenance of phospholipid species that are critical for phagocytosis, as is the case of the phosphoinositides; the existence of phospholipid pools of species with still undefined roles such as the ethanolamine plasmalogens. These can assist phagocytosis or affect membrane fluidity or, in their oxidized form, be involved in important functions such as ferroptosis. Thus, orchestration of a full innate immune response could be contemplated as a miscellany of lipid molecules, pathways and chemical interactions, in which many single molecular species have a role in the promotion and/or resolution of inflammation. Much of this recently unveiled lipid signaling involves the modulatory action of iPLA$_2$β. Thus this enzyme has emerged as a common regulatory link between homeostatic lipid metabolism, redox biology and disease, and as such, it may be of great interest for inflammatory drug development and therapeutics.

Author contributions

Conceptualization: A.M.A., M.A.B., and J.B; Funding acquisition: M.A.B., and J.B.; Project administration: M.A.B., and J.B.; Writing-original draft: A.M.A., M.A.B., and J.B.; Writing-review & editing: A.M.A., M.A.B., and J.B.

Declaration of Competing Interest

The authors declare no conflict of interest.

Data availability

No data was used for the research described in the article.

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