Lysophospholipid acyltransferases and leukotriene biosynthesis: intersection of the Lands cycle and the arachidonate PI cycle

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Abstract  Leukotrienes (LTs) are autacoids derived from the precursor arachidonic acid (AA) via the action of five-lipoxygenase (5-LO). When inflammatory cells are activated, 5-LO translocates to the nuclear membrane to initiate oxygenation of AA released by cytosolic phospholipase A2 (cPLA2) into leukotriene A4 (LTA4). LTA4 can also be exported from an activated donor cell into an acceptor cell by the process of transcellular biosynthesis. When thimerosal is added to cells, the level of free AA increases by inhibition of lysophospholipid acyltransferases of the Lands pathway of phospholipid remodeling. Another arachidonate phospholipid cycle involves phosphatidylinositol (PI) in the plasma membrane that undoubtedly intersects with the Lands pathway of phospholipid remodeling. The highest abundance of PI occurs between the ER and the plasma membrane and is probably a result of the importance of the PI signaling cascade in cellular biochemistry. Because transport proteins mediate the rapid intracellular movement of phospholipids, largely as result of physical membrane contact, 5-LO-dependent production of LTA4 could be mediated by the disappearance of free AA from the nuclear membrane, transfer to the ER for Lands cycle reesterification into PI, and population of PI(18:0/20:4) for cell membrane signaling.

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Considerable information is now available concerning the complexity of biochemical events that take place leading to the synthesis of leukotrienes (LTs), which are lipid mediators derived from arachidonic acid (AA). However, important questions remain concerning LT biosynthesis before a complete description of the function that leukotrienes play in both human health and disease can be made.

With our expanding understanding that inflammation plays critical roles in multiple disease processes, leukotrienes continue to be recognized as important substances to consider in events taking place in pathophysiology. Leukotrienes

Abbreviations: AA, arachidonic acid; ACSL, acyl CoA synthase; cPLA2, cytosolic phospholipase A2; IP3, inositol trisphosphate; LO, lipoxygenase; LPCAT, lysophospholipid acyltransferase; LT, leukotriene; PI, phosphatidylinositol; PIP2, PI-4,5P2; 1To whom correspondence should be addressed.
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are the result of several steps of enzymatic processing of the initial, chemically unstable leukotriene \( \text{A}_4 \) (LTA\(_4\)). LTA\(_4\) is the direct chemical precursor of leukotriene \( \text{B}_4 \) (LTB\(_4\)), a chemotactic lipid (1, 2), or leukotriene \( \text{C}_4 \) (LTC\(_4\)) and peptide cleavage products leukotriene \( \text{D}_4 \) (LTD\(_4\)) and leukotriene \( \text{E}_4 \) (LTE\(_4\)), which constitute the biological activity termed slow reacting substance of anaphylaxis (3). Therefore, investigations into the basic biochemistry engaged in leukotriene biosynthesis, release of these specific lipids from the cell, and intracellular signaling events initiated from leukotriene receptor occupation continue to be important.

Five-lipoxygenase (5-LO) is a nonheme iron dioxygenase, with a C-2 domain at the N terminus and an active site C terminus made up of \( \alpha \)-helices, that stereospecifically attaches diatomic oxygen to the 5-carbon position of free AA. Specific details concerning structure of this enzyme and the nature of the histidine coordination of iron (4), redox changes that occur during the lipoxygenase reaction (5), sites for protein phosphorylation (6, 7), as well as substrate binding (4) are now known. There is limited expression of the gene that codes for 5-LO, which is somewhat restricted to inflammatory cells such as neutrophils, mast cells, eosinophils, macrophages and basophils. There is some evidence that 5-LO can be expressed in virus- and cancer-transformed cells (8, 9). In the context of this review, it is important to consider that 5-LO is typically, but not exclusively, found in the cytosol of cells that express the 5-LO gene. For the enzymatic reaction to proceed, cytosolic 5-LO must be translocated to the perinuclear membrane. This translocation event is a result of the elevation of intracellular calcium ions also required to activate the enzyme 5-LO. Recent studies have suggested that the translocation process is mediated by a coactosin-like protein that binds 5-LO as well as F-actin and calcium ions critical for translocation and 5-LO activation (10). This elevation of intracellular calcium ion is the result of many different types of cell stimulation that initiate leukotriene biosynthesis. Once at the nuclear envelope, a second binding protein, termed five-lipoxygenase activating protein, is engaged and thought to act as a scaffolding protein (11) as well as presenting AA to the catalytic site of 5-LO.

In addition to elevated calcium ions, free AA must appear within the nuclear membrane bilayer as the required substrate for 5-LO. This elevation of free AA at the nuclear dual bilayer is a result of the action of phospholipase A2 that hydrolyzes esterified arachidonate at the sn-2 position of phospholipids. There are a large number of phospholipase A2s (12) and likely multiple enzymes are engaged in the series of events that result from liberation of free AA. It is now recognized that a cytosolic phospholipase A2, cPLA2\(_{a}\), is critical for the biosynthesis of leukotrienes (13). Cytosolic cPLA2\(_{a}\) is also translocated to the nuclear envelope, a result of elevation of intracellular calcium during cell stimulation. A typical pathway summary for leukotriene biosynthesis is diagrammed in Fig. 1, but this is known to be a rather oversimplification of the complexity of events that actually take place leading to the activation of 5-LO, translocation and conversion of free AA into leukotriene \( \text{A}_4 \) at the nuclear bilayer.

In addition to the requirements for calcium ion elevation and free AA, 5-LO activity can be regulated by protein phosphorylation at Ser271 (MAPKAP kinase site), Ser663 (ERK2 site), and Ser523 (PKA site) (6, 7). The latter site reduces activity of 5-LO in a cAMP dependent manner, likely by altering translocation of 5-LO to the nuclear membrane (14). Thus, agents that affect cAMP, such as adenosine (15), steroids (16), and \( \beta_2 \) adrenergic agonists (17), can reduce production of leukotrienes, as has been known for some time (18).

The production of specific leukotrienes, such as LTB\(_4\) or LTC\(_4\), is the result of enzymatic conversion of LTA\(_4\) (the direct 5-LO product) by leukotriene \( \text{A}_4 \) hydrolase (19) and leukotriene \( \text{C}_4 \) synthase (20), respectively. LTC\(_4\) synthase also requires a cosubstrate, the tripeptide GSH. Once synthesized, these lipids leave the cytosol (LTB\(_4\)) or nuclear membrane (LTC\(_4\)), likely mediated by a transport carrier, and exit the cell, where they can bind to a specific G-protein membrane receptor to elicit a biological action. Peptidases are responsible for cleavage of the GSH tripeptide into LTD\(_4\) and LTE\(_4\) as the result of a specific \( \gamma \)-glutamyl transpeptidase (21) and a unique dipeptidase (22). Expression of these auxiliary enzymes is an important determinant of which specific leukotriene is made by an individual cell and, therefore, the biological activities that result from activation of the 5-LO pathway in a tissue.

**TRANSCELLULAR BIOSYNTHESIS**

A rather unexpected mechanism by which leukotrienes appear in a tissue is that of movement of newly synthesized LTA\(_4\) from the activated cell that expressed 5-LO into a cell that contains one of the auxiliary enzymes, such as LTC\(_4\) synthase or LTA\(_4\) hydrolase (23). This is the process of transcellular biosynthesis. The curious feature of such events is that LTA\(_4\) is a conjugated triene epoxide and as such, quite chemically reactive. This epoxide has been suggested to have a chemical half-life under 1 s (24). Considering that LTA\(_4\) is made at the nuclear envelope, it must cross not only the cytosol but also at least two plasma membranes to find the site within another cell where LTA\(_4\) hydrolase or LTC\(_4\) synthase reside. For this lipid to survive the aqueous environment, it must be protected, most likely by protein binding in a hydrophobic pocket (Fig. 1). Several candidate proteins have been proposed (25), with the most effective stabilizing protein being albumin (24). Albumin is also shown to stabilize another very unstable AA-metabolite, i.e., thromboxane \( \text{A}_2 \) (26).

An interesting question that has emerged concerning transcellular biosynthesis is whether or not LTA\(_4\) is bound to a carrier protein in the extracellular media or, rather, whether cell-cell contact is required for a stabilizing protein to transfer LTA\(_4\) into a recipient cell. In experiments attempting to address this question, various antibodies to one potential carrier protein, complex S100 A8/A9 (27), were added to suspensions of human neutrophils to trap any extracellular LTA\(_4\) bound to these proteins. The result of these experiments was unexpected in that, rather than
increasing the amount of nonenzymatic transformation of LTA₄ into 6-trans LTB₄, the total synthesis of LTB₄ increased almost 50-fold. Such a promotion of stimulated leukotriene biosynthesis had never been previously observed, requiring some understanding of the mechanism by which this occurred. After considerable effort, it was found that the antibody itself was not involved, but, rather, a preservative in the antibody preparation was responsible for this stimulation of leukotriene biosynthesis. This preservative was thimerosal, an organomercury reagent (ethyl (2-mercaptobenzoato- (2)-O,S) mercurate), used in the past to preserve vaccines. It was found that thimerosal substantially increased the level of free AA in stimulated macrophages and neutrophils, likely by inhibiting a lysophosphatidylcholine acyltransferase (LPCAT) responsible for the conversion of arachidonoyl CoA into an arachidonate containing phospholipid (28). The unexpected nature of this serendipitous finding revealed the involvement of the reacylation pathway termed the Lands pathway (29) in leukotriene biosynthesis. Thimerosal had been previously suggested to inhibit lysophosphatidylcholine acyltransferase as well as transacylases (30–32). A detailed understanding of exactly which LPCATs were present in the human neutrophils was at that time unknown.

**LPCATs**

The Lands pathway involves remodeling of phospholipids synthesized by the normal Kennedy pathway, which generates saturated and monounsaturated fatty acyl groups on the various phospholipid backbones (Fig. 2). In order to incorporate polyunsaturated fatty acids derived from the diet into phospholipids, a phospholipase A₂ cleaves the
fatty acyl group from the sn-2 position of the de novo synthesized phospholipid forming a lysophospholipid for each of the choline-, inositol-, ethanolamine-, glycerol-, and serine-phospholipid classes, then arachidonoyl CoA is covalently bound to the lysophospholipid through the action of one or more LPCATs.

There are numerous LPCATs (33), each with somewhat specific roles for the formation of specific phospholipid molecular species, including polyunsaturated fatty acyl containing phospholipids. The fatty acyl CoA ester is derived from the free fatty acid covalently linked as a thioester to CoA by a long chain-fatty acyl CoA synthase (ACSL) in a two-step mechanism (34). There are several families of these synthases known to be present in mammalian cells and responsible for the formation of the various long chain fatty acyl CoA esters. Although ACSLs appear to have considerable promiscuity, some experiments suggest that ACSL-4 is somewhat specific for formation of arachidonate CoA esters (35). In addition to the synthases, there are also fatty acyl CoA hydrolases, which hydrolyze the CoA esters back to the free fatty acids (36). The fatty acyl CoA thioesters are engaged in many lipid biosynthetic reactions including neutral lipid formation, such as cholesteryl ester, and triacylglycerol biosynthesis (37). The fatty acyl CoA thioesters are also required for β-oxidation, either in the mitochondria or peroxisome (38). Polyunsaturated fatty acyl CoA esters are the required substrates of LPCATs along with a lysophospholipid in the synthesis of a polyunsaturated phospholipid molecular species.

The LPCAT genes expressed in the human neutrophil are MBOAT1, MBOAT2, MBOAT5, and MBOAT7 (39). Alternative designation of these genes have been recently suggested as LPEAT1, LPCAT4, LPCAT3, and LPIAT, respectively (40). The substrate specificity of these enzymes was investigated using a novel substrate competition assay that involved incubation of a mutant yeast (Ale1 deficient) engineered to express each of these human MBOATs with six different fatty acyl CoA esters and eight different lysophospholipid substrates in a single in vitro assay. Because the mutant yeast (Ale1) lacked any lysophospholipid acyltransferase activity, this experiment revealed which substrates each human LPCAT preferred. The results were fascinating in that two enzymes were found to be rather specific for AA incorporation into phospholipids, LPCAT3/MBOAT5 and MBOAT7 (39).

**Fig. 2.** Incorporation of arachidonic acid into membrane-bound phospholipids by the Lands pathway (28). Free AA is converted to the CoA ester and then a substrate for lysophospholipid acyltransferases located in the ER for incorporation into membrane phospholipids. The free AA can also be a substrate for various oxidation reactions to form bioactive eicosanoids or β-oxidation, while CoA esters can be substrates for acyltransferases to form cholesteryl esters or diacyl- and triacylglycerols.

**LPCAT AND LEUKOTRIENE BIOSYNTHESIS**

The question of whether or not an LPCAT can control leukotriene biosynthesis has been addressed using several different experimental approaches. As discussed above, the drug thimerosal had a profound effect on increasing leukotriene A₄ biosynthesis in the human neutrophil. Lipidomic analysis revealed substantial changes in neutrophil phospholipid molecular species containing arachidonate after thimerosal exposure (unpublished observations). In an experiment designed to probe the effect of a chronic loss of one LPCAT specific for arachidonate remodeling, a lentivirus shRNA was used to knock down LPCAT3/MBOAT5 in RAW264.7 cells (41). Following cell stimulation, phospholipid molecular species, free AA, and LTC₄ analysis was carried out. Three different shRNA constructs were made that reduced the expression of LPCAT3/MBOAT5. Lipidomic analysis of the control and knockdown cells revealed substantial decrease in arachidonate-PE as well as arachidonate-PC as expected (supplemental Fig. S1). However, only one of the shRNA constructs (construct number 1) altered the production of LTC₄ (supplemental Fig. S2) after stimulation with 3 mM ATP for 15 min. There was no change in the expression of ACSL, 5-LO, or cPLA2 in these LPCAT3/MBOAT5 knockdown RAW cells (41). Overall, the results of these experiments were somewhat unexpected in that there did appear to be major change in PE and PC phospholipid remodeling, but there was not a significant change in production of LTC₄.

PI molecular species containing arachidonate, however, were not significantly altered in these knockdown cells.

**ARACHIDONATE PI CYCLE**

Based on a large number of mass spectrometric-based lipidomic studies, the major molecular species of PI observed in mammalian cells appears at m/z 885.5494, the negative ion corresponding to PI(38:4), which has been analyzed by tandem mass spectrometry and identified as...
PI(18:0/20:4) (42). However, in almost all lipidomic studies, subcellular location of PI molecular species is not examined, but, rather, total cellular PI molecular species reported. Yet, considerable interest in PI has focused on the plasma membrane where receptor signaling events take place. Formation of second messengers are derived from PI-4,5P2 (PIP2) by the action of phospholipase C, which catalyzes the hydrolysis of this phospholipid into inositol trisphosphate (IP3) and diacylglycerol that then appear at the plasma membrane (Fig. 3) (43). These facts support the concept that another important arachidonate phospholipid cycle exists, one that involves the plasma membrane PI(18:0/20:4)-4,5P2. This phosphoinositol molecular species is formed from PI(18:0/20:4) made in the ER/trans Golgi by phosphatidylinositol synthase then transported to the plasma membrane, where phosphorylation occurs by two kinases, PI4 kinase and PI4P-5 kinase (44). After release of IP3, the diglyceride, DG (18:0/20:4), is transported back to the ER/trans Golgi (45) and phosphorylated to form the phosphatidic acid molecular species that is subsequently converted to CDP-DG (18:0/20:4), thus completing the arachidonate PI cell cycle.

The initial appearance of AA in this arachidonate PI cycle is undoubtedly a result of intersection of this pathway with the Lands pathway of phospholipid remodeling, residing also at the ER. MBOAT7 in the ER/trans Golgi specifically binds arachidonoyl-CoA ester to lyso PI(18:0) to form the abundant molecular species PI(18:0/20:4). Formation of lyso PI(18:0) would involve one or more phospholipase A2 species at the ER or even the nuclear membrane. Previous work has found that the subcellular location of PI molecular species is not uniform. The highest abundance of PI is found divided between the ER and the plasma membrane, and very small amounts at the nuclear membrane (supplemental Fig. S3) (46). This very high level of PI in the plasma membrane is probably a consequence of the importance of the PI signaling cascade in cellular biochemistry. The importance of PI to the signaling cascade has also been suggested by the failure of MBOAT7 knockout mice to survive (47).

PHOSPHOLIPID MOVEMENT TO INTRACELLULAR ORGANELLES

It is widely appreciated that de novo phospholipid biosynthesis and the Lands cycle remodeling pathway are restricted to the intracellular ER location (29). Once the synthesis and remodeling of phospholipids into new molecular species has taken place, these phospholipids find their way to various organelles such as the plasma membrane and nuclear membranes suggested by the rather simplistic diagrams presented above (Figs. 2, 3). Yet, phospholipids and even fatty acids are poorly soluble in water and thus unlikely to diffuse by passive mechanisms, certainly not in a rapid fashion. Rather, it is becoming increasingly clear that protein-mediated events are involved to rapidly move lipids between various subcellular organelles. A host of proteins are known to be involved in this process of insoluble lipid movement within the cell. For example, fatty acids are transported by binding protein such as fatty acid translocases (FAT/CD36), fatty acid binding proteins, fatty acid transport proteins, as well as ubiquitous proteins such as intracellular albumin (48). The mechanism of protein-mediated transfer of intact phospholipids has been suggested to be largely the result of physical membrane contact (49).

The consequence of protein involvement in membrane-associated transfer of fatty acid and phospholipid molecular...
species is that each organelle has a unique phospholipid composition at any one time. Phospholipid molecular species and free fatty acids are not in chemical equilibrium within the cell, and the disequilibrium is maintained through protein binding and transfer, likely through direct organelle contact.

The stimulation of leukotriene production in cells treated with thimerosal implies that a substantial concentration of free AA appears rapidly in the nuclear membrane, the site in which 5-LO forms LTA₄. This excess free AA, as well as the lysophospholipids formed by the action of phospholipase A2, under normal circumstances would be immediately transported to the ER where there is enzymatic activity for remodeling by the Lands cycle (LPCATs and ACSL to form arachidonoyl CoA). However, when thimerosal is present to inhibit ER LPCATs, the level of free AA and arachidonoyl CoA increase in the ER, which slows transfer of nuclear membrane free AA. Thus, at the nuclear membrane, free AA increases dramatically. Interestingly, it had never been appreciated that 5-LO-mediated production of LTA₄ could be mediated by the disappearance of free AA from the nuclear membrane and transfer to the ER for Lands cycle reesterification. Disruption of these lipid transport events and altered arachidonoyl CoA concentration at the ER permitted uncontrolled LTA₄ formation due to the continued high abundance of free AA within the nuclear membrane.

In terms of knockdown experiments or specific inhibition of one acyltransferase activity, the buildup of free AA in the ER would be unlikely because multiple enzymes are present there to use the excess arachidonoyl CoA as a substrate. Specifically, in the MBOAT5 knockdown experiments, the PI(18:0/20:4) synthesis and active MBOAT7 remain in place at the ER to use excess arachidonoyl CoA derived from the cPLA2 release of AA at the nuclear membrane. Any specific decrease in MBOAT7 activity at the ER would be expected to result in a reduction of LTA₄ formation by a decrease in nuclear membrane PI(18:0/20:4) content, but certainly not an increase of LTA₄ formation observed in the thimerosal experiments where multiple LPCATs were inhibited.

We suggest that arachidonate-containing PI (PIP and PIP₂) abundance at the plasma membrane is maintained at the expense of the ER/trans Golgi and nuclear membrane arachidonate-PI that is needed for proper functioning of the signaling events at the plasma membrane. A complex interplay of the Lands cycle at the ER likely exists that populates arachidonate into all phospholipid classes with the arachidonate-PI cycle, PIP and PIP₂ at the plasma membrane, and PI(18:0/20:4) within the nuclear membrane of the cell (Fig. 4). Therefore, when the plasma membrane becomes depleted of PIP and PIP₂ as a result of sustained signaling events at that site, the nuclear membrane and ER supply necessary PI (18:0/20:4). This could reduce the capacity of this cell to synthesize leukotrienes at the nuclear membrane. Alternatively, with sufficient and even excess arachidonate, when the Lands pathway is inhibited, much more substrate arachidonate is available at the nuclear membrane to drive leukotriene biosynthesis. Because the lowest abundance of arachidonate-PI found at subcellular locations is at the nuclear membrane, this one site would likely be the most sensitive to depletion. Regulation of the production of LTC₄ by operation of the complex interaction of the AA remodeling cycle in the nuclear membrane/ER (Lands pathway) and the second messenger PI cycle located in the plasma membrane/ER suggests a very important interaction between the LPCATs and the leukotriene biosynthetic machine as a result of the subcellular

![Diagram of Arachidonate PI Cycle and Lands Cycle](https://example.com/diagram.png)

**Fig. 4.** Suggested interaction of the arachidonate PI cycle (ER and plasma membrane) with the Lands cycle (ER and nuclear membrane) that could regulate cellular leukotriene biosynthesis. These events occur in different subcellular locations. If the specific LPCAT for PI biosynthesis (MBOAT7/LPIAT) located in the ER is reduced in activity, the plasma membrane is not spared of PI(18:0/20:4) to generate PIP₂, but the biosynthesis of leukotrienes decreases due to a decrease in PI(18:0/20:4) at the nuclear membrane.
location of individual molecular species of phospholipids and corresponding enzymes and transport proteins.

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