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Introduction to Thematic Review Series: Phospholipases: Central Role in Lipid Signaling and Disease

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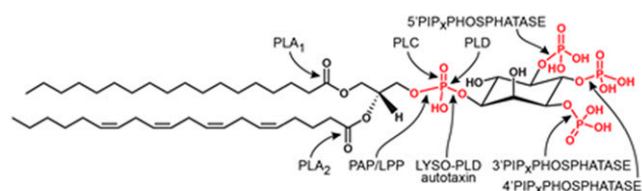
PHOSPHOLIPID HYDROLASES

Hydrolases constitute an enormous proportion of our enzymes, being responsible for the initiation of most digestive processes and numerous physiological processes. They are defined as enzymes that use a molecule of water to degrade substrates including all four kinds of biological molecules; namely, nucleic acids (nucleases), proteins (proteases), lipids or fats (lipases), and carbohydrates or sugars (glycosidases). They include large families of acyl ester hydrolases, phosphate, pyrophosphate ester and diester hydrolases, and amide ester hydrolases.

Phospholipases constitute a class of hydrolases that catalyze the hydrolysis of acyl esters (deacylase activity) and phosphate esters (phosphodiesterase or phosphomonoesterase, also known as phosphohydrolase or phosphatase activity or sometimes pyrophosphatase activity) on phospholipids (diacylglycerophosphate esters and related compounds) (1). Phospholipases are defined by the position they hydrolyze on the phospholipid backbone as shown in **Fig. 1**. Of course, many enzymes are named based on the initial assay used to discover or define their activity and then are later discovered to exhibit additional activities, and often their predominant physiological activity is quite different than their name implies. Also, there are certainly many enzymes not named as phospholipases that exhibit phospholipase activity, sometimes as a side or minor activity when presented with the appropriate phospholipid substrate.

Sphingolipids constitute a separate category of lipids from phospholipids (2, 3), yet they reside similarly in membranes and functionally often play similar roles to phospholipids with some overlapping biosynthetic pathways. Some of the enzymes that hydrolyze sphingolipids carry out similar reactions to the phospholipases, such as sphingomyelinase, which exhibits a phospholipase C activity toward sphingomyelin, but additionally there are deamidases that hydrolyze the acyl amide on the ceramide backbone of sphingolipids and glycosidases that hydrolyze carbohydrates of glycosphingolipids. Such enzymes are not

Phospholipases



1-stearoyl,2-arachidonoyl phosphatidylinositol-3',4',5'-triphosphate (PIP₃)

Fig. 1. Site of hydrolase activity by phospholipase A₁ (PLA₁), phospholipase A₂ (PLA₂), phospholipase C (PLC), phosphatidic acid phosphatase (PAP)/lipid phosphate phosphatase (LPP), phospholipase D (PLD), lysophospholipid phospholipase D (LYSO-PLD, also known as autotaxin), and phosphatidylinositol polyphosphate phosphatase (PIP_x phosphatase) which can be specific for the 3', 4' or 5' position shown on a typical phospholipid, 1-stearoyl,2-arachidonoyl-phosphatidylinositol-3',4',5'-triphosphate (PIP₃).

included in this Thematic Review Series but are reviewed elsewhere (4).

PHOSPHOLIPASES ACT ON MEMBRANE/MICELLAR PHOSPHOLIPID SUBSTRATES

Phospholipases are major digestive enzymes and play a critical role in most physiological processes including the generation of numerous signaling lipids, and in aggregate, seem to affect all diseases in some manner. The phospholipid substrates generally exist in membranes or micelles due to their amphipathic character or low critical micelle concentration (CMC), yet the phospholipase enzymes can be either water-soluble and can associate with membranes/micelles to find their substrates or they may be membrane-bound proteins with an intimate supply of substrate. Thus, because phospholipases differ dramatically from “normal”

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water-soluble enzymes that bind water-soluble substrates in solution, special interfacial kinetics must be taken into account in studying phospholipases (5).

Phospholipases by definition must find their substrates that reside in a membrane or micelle, so the enzymes generally must first associate with the membrane or micelle and often are membrane-bound. The most detailed description of how a phospholipase acts to associate with a membrane and then to sequester its substrate phospholipid molecule in its active site has been developed for phospholipase A₂ (PLA₂) utilizing deuterium exchange mass spectrometry (6) to elucidate the interactions for docking and molecular dynamics to refine the structure, as illustrated in Fig. 2 (7).

PHOSPHOLIPASE FOCUS

This series will begin with a consideration of an acyl hydrolase specific for the *sn*-2 position (stereospecific nomenclature) of the glycerolphosphate backbone of phospholipids, phospholipase A₂, because that is the most well studied phospholipase and actually consists of a superfamily of enzymes including some 16 groups and many subgroups representing six main types of PLA₂ (8). The secreted PLA₂s are among the most well studied as they have been known for over a century from studies on snake venom and the pancreatic digestive enzyme, and many mechanistic and inhibitory studies have been carried out on their numerous isoforms.

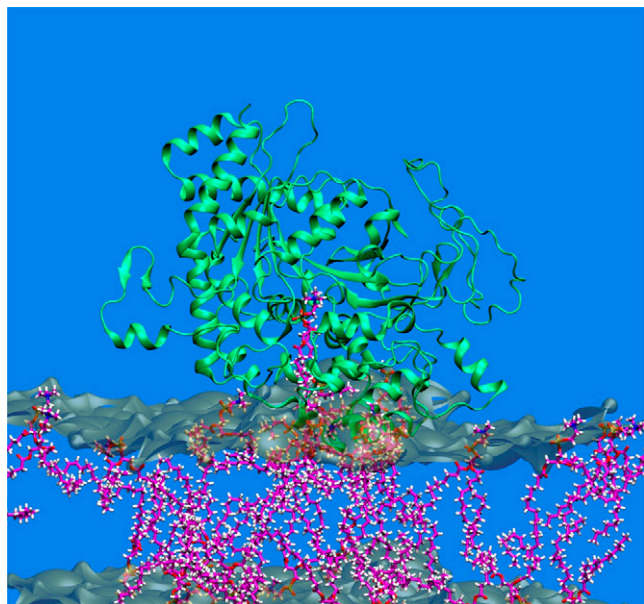


Fig. 2. A phospholipase typically associates with a membrane and then sequesters a phospholipid substrate molecule in its catalytic site to carry out hydrolysis. The catalytic domain of human cPLA₂ based on its crystal structure is shown optimized after extracting a typical substrate 1-palmitoyl,2-arachidonoyl phosphatidylcholine (PAPC) molecule into its catalytic site from the membrane containing 1-palmitoyl,2-oleoyl phosphatidylcholine (POPC) bilayers based on extensive molecular dynamics simulations. Adapted from (7).

In the first review in this series, which appears in this issue of the *Journal of Lipid Research*, Makoto Murakami and colleagues from the Tokyo Metropolitan Institute of Science describe “A new era of secreted phospholipases A₂ (sPLA₂)” (9). This will be followed with a review on “Cytosolic phospholipase A₂: physiological function and role in disease” by Christina Leslie from the National Jewish Health Sciences in Denver (10), which will appear in the August issue. In the September issue will be a review by Sasanka Ramanadham and collaborators from the University of Alabama at Birmingham on “Calcium-independent phospholipases A₂ (iPLA₂s) and their roles in biological processes and diseases” (11).


The fourth type of PLA₂ is PAP-acetyl hydrolase (PAFAH), also known as lipoprotein-association phospholipase A₂ (Lp-PLA₂), and this enzyme has been considered recently in the *Journal* by Diana Stafforini and Guy Zimmerman from the University of Utah (12). The lysosomal phospholipase A₂ (L-PLA₂) and the adipose phospholipase A (A-PLA₂) have been less well studied than the other four types and are included in a recent comprehensive review on phospholipases A₂ (8). As hydrolytic enzymes, the PLA₂s are not just degradative and signaling enzymes, as some of them play an important functional role in producing the lysophospholipid substrate for acyl transferases to produce remodeled phospholipids containing a polyunsaturated fatty acid in their *sn*-2 position. Describing a more physiological setting, Nicolas Bazan from the Louisiana State University in New Orleans will describe recent work on the remodeling of phospholipids to become enriched in the omega-3 fatty acid docosahexenoic acid (DHA) and very long chain polyunsaturated fatty acids, as well as the role of these phospholipids in photoreceptor cell function and retinal degeneration.

Phospholipase A₁ (PLA₁) hydrolyzes the acyl chain on the *sn*-1 position of phospholipids. Hiroyuki Arai from the University of Tokyo and Junken Aoki from Tohoku University will review our current knowledge about phospholipase A₁, including its biology and pathology.

Phosphohydrolases can cleave phospholipids on the glycerol side of the phosphodiester bond defined as phospholipase C (PLC), as reviewed by Lucio Cocco and collaborators from the University of Bologna on those PLCs acting on phosphatidylinositol polyphosphates in their article titled “Phosphoinositide-specific phospholipase C (PI-PLC) in health and disease” (13). Relatedly, David Brindley and colleagues from the University of Alberta in Edmonton review lipid phosphate phosphatase (LPP), also referred to as phosphatidic acid phosphatase (PAP2), in their paper, “Lipid phosphate phosphatases and their roles in mammalian physiology and pathology” (14). Importantly, members of this family hydrolyze phosphatidic acid (PA), lysophosphatidic acid (LPA), sphingosine-1-phosphate (S1P), ceramide-1-phosphate (C1P), and diacylglycerol pyrophosphate (DGPP), all of which are important signaling lipids. Phosphatidic acid phosphatase 1 (PAP1), which is also known as “lipin”, has been reviewed previously by Karen Reue and Jennifer R. Dwyer from the University of California, Los Angeles in the *Journal* (15).

Phosphohydrolases that cleave phospholipids on the polar or distal side of the phosphodiester bond are called phospholipase D (PLD), and are reviewed by Michael Frohman and his colleague at the State University of New York in Stony Brook in their article “Physiological and pathophysiological roles for phospholipase D” (16). Gordon Mills and colleagues at the MD Anderson Cancer Center at the University of Texas in Houston have reviewed those PLD enzymes acting on lysophospholipids in their paper titled “Autotaxin, a lysophospholipase D with pleomorphic effects in oncogenesis and cancer progression” (17).

Finally, phospholipases generally referred to as phosphatases can hydrolyze the various phosphate esters on specific positions on the inositol sugar attached to phosphatidylinositol polyphosphates, and Michael Wakelem and colleagues from the Babraham Institute in Cambridge will describe the various phosphatidylinositolphosphate phosphatases and cancer.

In this Thematic Review Series, we include for each type of phospholipase the reaction it primarily carries out, noting secondary reactions, the names (Group numbering or other system, systematic name, and common names), primary sequence differences between the various forms and homologs, three-dimensional structure(s) when crystal structures are solved, the biological functions, and the disease implications. All of the identified enzymes of the type covered by the review are summarized, though the reviews generally focus on the major form(s) that have been most well studied and their signaling function and disease implications. 

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