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Review

Properties of the Group IV phospholipase A_2 family

Moumita Ghosh [a], Dawn E. Tucker [a], Scott A. Burchett [a], Christina C. Leslie [a,b,*]

[a] *Department of Pediatrics, National Jewish Medical and Research Center, 1400 Jackson Street, Denver, CO 80206, USA*
[b] *Departments of Pathology and Pharmacology, University of Colorado School of Medicine, Aurora, CO 80045, USA*

Abstract

The Group IV phospholipase A_2 family is comprised of six intracellular enzymes commonly called cytosolic phospholipase A_2 (cPLA$_2$) α, cPLA$_2$β, cPLA$_2$γ, cPLA$_2$δ, cPLA$_2$ε and cPLA$_2$ζ. They are most homologous to phospholipase A and phospholipase B/lysophospholipases of filamentous fungi particularly in regions containing conserved residues involved in catalysis. However, a number of other serine acylhydrolases (patatin, Group VI PLA$_2$s, *Pseudomonas aeruginosa* ExoU and NTE) contain the Ser/Asp catalytic dyad characteristic of Group IV PLA$_2$s, and recent structural analysis of patatin has confirmed its structural similarity to cPLA$_2$α. A characteristic of all these serine acylhydrolases is their ability to carry out multiple reactions to varying degrees (PLA$_2$, PLA$_1$, lysophospholipase and transacylase activities). cPLA$_2$α, the most extensively studied Group IV PLA$_2$, is widely expressed in mammalian cells and mediates the production of functionally diverse lipid products in response to extracellular stimuli. It has PLA$_2$ and lysophospholipase activities and is the only PLA$_2$ that has specificity for phospholipid substrates containing arachidonic acid. Because of its role in initiating agonist-induced release of arachidonic acid for the production of eicosanoids, cPLA$_2$α activation is important in regulating normal and pathological processes in a variety of tissues. Current information available about the biochemical properties and tissue distribution of other Group IV PLA$_2$s suggests they may have distinct mechanisms of regulation and functional roles.

Keywords: Phospholipase A2; C2 domain; Calcium; Eicosanoids; Arachidonic acid; Catalytic dyad

Contents

* Corresponding author. Address: Department of Pediatrics, National Jewish Medical and Research Center, 1400 Jackson Street, Denver, CO 80206, USA. Tel.: +1 303 398 1214; fax: +1 303 270 2155.
E-mail address: lesliec@njc.org (C.C. Leslie).

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1. Introduction

Mammalian cells contain a large number of phospholipases that hydrolyze phospholipid in a structurally specific manner for production of a myriad of products, many of which have potent biological activity. There are hundreds of phospholipid molecular species in cells that are differentially localized in subcellular organelles, on different leaflets of membranes, and within lateral phases of membrane bilayers [1,2]. Phospholipids are dynamic molecules that can flip at different rates between membrane leaflets and diffuse laterally within the bilayer. The asymmetric distribution of phospholipid molecular species in membrane leaflets is enzymatically regulated by phospholipid flippases, floppases and scramblases [3,4]. The action of phospholipases at specific subcellular locations can promote the formation of unique phospholipid breakdown products that affect cell and organelle function. Phospholipases produce both hydrophobic and water soluble mediators that can act at the site of production in the membrane, at distal sites within the cell, or extracellularly upon secretion. Many products of phospholipid breakdown mediate cellular function by acting through extracellular or intracellular receptors [5–7]. Additionally, the regulated hydrolysis of phospholipids affects the physical properties of membranes that may influence cell shape, motility, and endocytic and secretory processes. Thus, the breakdown of specific phospholipid molecular species at different sites within cells by phospholipases plays a fundamental role in cell function.

Phospholipid acyl chains are continuously turning over and being remodeled. This occurs at both the *sn*-1 position (enriched in saturated fatty acids) and the *sn*-2 position (enriched in unsaturated fatty acids) of phospholipids [8,9]. The specific deacylating phospholipases A (PLA), and reacylating acyltransferases and transacylases, involved in this constitutive process have remained largely unidentified at the primary sequence level. However, biochemical studies indicate the involvement of multiple substrate selective forms of coordinately acting phospholipases and acyltransferases [8,10]. The turnover of phospholipid acyl chains functions in part to repair membranes by removing oxidized fatty acids, and for formation of specific phospholipid molecular species such as those containing *sn*-2 arachidonic acid and *sn*-2 palmitic acid. In addition to constitutive acyl chain turnover, PLA enzymes are involved in the regulated release of fatty acyl chains from phospholipids resulting in formation of biologically active lipid mediators. The direct products of PLA action, fatty acids and lysophospholipids, are themselves potential mediators or serve as precursors of bioactive molecules, such as eicosanoids and platelet-activating factor, respectively [11,12]. All cells contain PLA$_1$ activities but only recently have PLA$_1$s that produce lysophospholipid mediators been characterized. PLA$_1$s specific for phosphatidic acid and phosphatidylserine have been cloned and these enzymes are implicated in the production of the lipid mediators 1-lyso-2-acyl-phosphatidic acid and 1-lyso-2-acyl-phosphatidylserine, respectively