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Mini-review

Emerging roles of secreted phospholipase A_2 enzymes: An update

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ABSTRACT

Phospholipase A_2 (PLA_2) enzymes catalyze the hydrolysis of the *sn*-2 position of glycerophospholipids to produce free fatty acids and lysophospholipids. More than one third of the mammalian PLA_2 enzymes belong to the secreted PLA_2 ($sPLA_2$) family, which consists of low molecular mass, Ca^{2+}-requiring enzymes with a His–Asp catalytic dyad. Individual $sPLA_2$ enzymes exhibit unique tissue and cellular localizations and specific enzymatic properties, suggesting their distinct biological roles. The past decade has met a new era of the $sPLA_2$ research field toward deciphering their *in vivo* functions by developing several specific tools and methods. These include i) the production of transgenic and knockout mouse lines for several $sPLA_2$s, ii) the development of specific analytical tools including the production of large amounts of recombinant $sPLA_2$ proteins, and iii) applying mass spectrometry lipidomics to unveil their specific enzymatic properties occurring *in vivo*. It is now obvious that individual $sPLA_2$s are involved in diverse biological events through lipid mediator-dependent and -independent processes, act redundantly or non-redundantly in the context of physiology and pathophysiology, and may represent potential drug targets or novel bioactive molecules in certain situations. In this review, we will highlight the newest understanding of the biological roles of $sPLA_2$s in the past few years.

1. Introduction

Mouse or human genomes encode genes for 11 to 12 secreted phospholipase A_2 ($sPLA_2$) enzymes (IB, IIA, IIC, IID, IIE, IIF, III, V, X, XIIA, XIIB and otoconin-90), which are subdivided into a conventional group (I, II, V, X and otoconin-90) and two atypical groups (III and XII) [1]. $sPLA_2$s have long been thought to act in a rather similar manner and to collectively participate in lipid digestion, host defense, inflammation and atherosclerosis. Recent studies using gene-manipulated mice for conventional (group IB, IIA, V and X) and atypical (III and XIIB) $sPLA_2$s have revealed their distinct contributions to these processes by degrading foreign phospholipids in bacterial membranes and foods, by modifying extracellular non-cellular lipid components (lipoproteins, lung surfactant, microparticles, etc), by producing lipid mediators from cellular membranes, or by unknown mechanism. The current understanding of the *in vivo* physiological and pathophysiological functions of $sPLA_2$s was summarized in our previous *Biochimie* review in 2010 [2] as well as in other recent reviews [3–5]. After publishing this review, significant advances in the $sPLA_2$ research field have been made, including additional insights into the pathophysiological roles of conventional $sPLA_2$s, but also some novel yet controversial actions of $sPLA_2$s in metabolic regulations, and the discovery of functions for atypical $sPLA_2$s. Here, we make a brief overview to update our understanding of the biological functions of mammalian $sPLA_2$s *in vivo*. Phenotypes of $sPLA_2$ gene-manipulated mice are summarized in Table 1.

2. $sPLA_2$s in innate and acquired immunity

Out of the different $sPLA_2$ isoforms, group V and X $sPLA_2$s have been shown to participate in the pathology of Th2-based asthma, since gene targeting of either of these two $sPLA_2$s in mice results in the amelioration of asthma models [6,7]. The attenuated asthmatic response in *Pla2g10*$^{-/-}$ mice is fully restored by knock-in of human group X $sPLA_2$, and treatment of the knock-in mice with a specific inhibitor of human group X $sPLA_2$ suppresses the airway symptoms [8]. As a possible mechanism, group X $sPLA_2$ is released from airway

Abbreviations: DHA, docosahexaenoic acid; DPA, docosapentaenoic acid; DRG, dorsal root ganglion; GI, gastrointestinal; LDL, low-density lipoprotein; LXR, liver X receptor; LPS, lipopolysaccharide; LPC, lysophosphatidylcholine; LPCAT, LPC, acyltransferase 1; PC, phosphatidylcholine; PLA_2, phospholipase A_2; PUFA, polyunsaturated fatty acid; $sPLA_2$, secreted PLA_2; Tg, transgenic; VLDL, very low-density lipoprotein; WT, wild-type.

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Table 1
Phenotype of $sPLA_2$ gene-manipulated mice (appropriate references can be found in the main text).

$sPLA_2$ collection	$sPLA_2$ subtype	Gene manipulation	Phenotype
Conventional $sPLA_2$s	IB	Knockout	Reduced obesity, hepatic steatosis and insulin resistance due to decreased phospholipid digestion in the GI tract
	IIA	Natural knockout	Increased colon cancer
		Knockout	Reduced arthritis
		Transgenic	Alopecia and epidermal hyperplasia
			Increased skin cancer[a]
			Increased atherosclerosis
			Protection from bacterial infection due to bacterial killing
	V	Transgenic	Neonatal death due to respiratory failure resulting from destruction of lung surfactant
		Knockout	Reduced zymosan-induced peritonitis
			Defective phagocytotic clearance of fungi
			Reduced asthma
			Impaired Th2 response[b]
			Reduced LPS-induced air pouch inflammation
			Reduced bacteria-induced airway inflammation
			Reduced ischemia/reperfusion-induced myocardial injury
			Reduced atherosclerosis[c]
			Exacerbated arthritis
	X	Transgenic	Pulmonary inflammation[d]
			Alopecia and epidermal hyperplasia
			Increased peripheral pain nociception
		Knockout	Reduced asthma
			Reduced ischemia/reperfusion-induced myocardial injury
			Reduced aneurysm
			Accelerated atherosclerosis[e]
			Reduced phospholipid digestion in the GI tract in association with reduced adiposity
			Abnormal hair follicles
			Reduced peripheral pain nociception
			Increased adiposity due to accelerated lipogenesis
			Increased adrenal corticosteroidogenesis
			Reduced macrophage cholesterol efflux
			Reduced LPS-induced cytokine production in macrophages
			Reduced capacitation of spermatozoa
Atypical $sPLA_2$ (group III collection)	III	Transgenic	Increased atherosclerosis
			Systemic inflammation
		Knockout	Impaired sperm maturation and infertility
Atypical $sPLA_2$s (group XII collection)	XIIB	Knockout	Steatohepatitis due to impaired hepatic secretion of VLDL

[a] Skin-specific.
[b] Adoptive transfer of dendritic cells.
[c] Adoptive transfer of bone marrow cells.
[d] Macrophage-specific.
[e] Bone marrow transfer into *Ldlr*$^{-/-}$ mice.

epithelial cells and may act on eosinophils in a paracrine manner to produce lysophosphatidylcholine (LPC), which in turn triggers Ca^{2+} influx leading to activation of cytosolic $PLA_2\alpha$ and thereby production of cysteinyl leukotrienes [9]. The mechanism for activation of group X $sPLA_2$ from its proenzyme form has not been elucidated in the lung tissue, but recent *in vitro* studies have shown that the proenzyme is converted during secretion by a furin-like proprotein convertase [10]. Of the three $sPLA_2$s (IIA, V and X) readily expressed in human lungs, group IIA and X enzymes are the major $sPLA_2$s that are increased in the bronchoalveolar lavage fluid of patients with asthma, where the levels of group X, but not group IIA, $sPLA_2$ appear to correlate with lung functions, neutrophil recruitment, and prostaglandin levels [11]. These results point to pulmonary group X $sPLA_2$ as a novel therapeutic target in asthma.

The action of group V $sPLA_2$ in asthma and other respiratory diseases seems to be more complex. The facts that group V $sPLA_2$ is induced in bronchial epithelial cells in antigen-challenged wild-type (WT) mice and that the intra-tracheal application of anti-group V $sPLA_2$ antibody ameliorates airway inflammation suggest a pro-inflammatory action of this enzyme in the airway [7]. Excessive hydrolysis of pulmonary surfactant by group V $sPLA_2$ perturbs the respiratory function in *Pla2g5*-transgenic (Tg) mice [12]. Insights into the surfactant hydrolysis by several $sPLA_2$s in acute respiratory distress syndrome have been documented in previous reviews [1,2,4]. Group V $sPLA_2$ is also localized in phagosomal membranes of macrophages [13]. Capture and processing of antigens by antigen-presenting cells are significantly attenuated in *Pla2g5*$^{-/-}$ mice, and accordingly, *Pla2g5*$^{-/-}$ mice display a reduction of Th2 polarization, thereby resisting subsequent propagation of asthmatic inflammation [14]. Thus, group V $sPLA_2$ appears to function on one hand in airway-resident cells to facilitate airway inflammation possibly via surfactant degradation and on another hand in antigen-presenting cells to regulate antigen processing and thereby the Th2 immune response. Deficiency of group V $sPLA_2$ reduces lipopolysaccharide (LPS)-induced leukocyte recruitment in an air pouch model [15]. Likewise, *Pla2g5*$^{-/-}$ mice are unable to properly eliminate *Escherichia coli* injected into the pulmonary tract likely because of the reduced recruitment of neutrophils, thereby suffering from severe respiratory acidosis and hypothermia [16]. As in the asthma model, group V $sPLA_2$ expressed in both myeloid cells and lung-resident non-myeloid cells participates in the innate immune response to pulmonary infection. Furthermore, *Pla2g5*$^{-/-}$ mice show reduced clearance of *Candida albicans* leading to severe systemic candidiasis [17] and that of immune complex leading to exaggerated inflammatory arthritis [18], revealing both anti-microbial and anti-inflammatory roles of group V $sPLA_2$ in these situations. Interestingly, treating mice with recombinant group V $sPLA_2$ has a protective effect against arthritis, supporting the concept that certain $sPLA_2$s may be bioactive and therapeutic molecules that should not be inhibited, but rather stimulated in specific inflammatory conditions.

Elucidating the functions of group IIA $sPLA_2$ in lung inflammation and more generally in innate and acquired immunity has largely been hampered by the marked differences in tissue distribution of this $sPLA_2$ between the mouse species and other species including rat and human among others. More specifically, it is believed that group IIA $sPLA_2$ plays an *in vivo* role in innate host defense against different strains of bacteria by directly hydrolyzing bacterial membranes in the lung of rat, guinea pig or human, but not mouse, where this $sPLA_2$ has never been detected [19]. Interestingly, different bacterial strains have developed counteracting mechanisms to circumvent the potent antibacterial activity of group IIA $sPLA_2$ [20,21]. Studying the *in vivo* function of group IIA $sPLA_2$ in host defense and inflammatory conditions has also been limited by the fact that inbred C57BL/6 and 129 mouse strains are