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Review

Phospholipase A_2 activities in skin physiology and pathology ☆

Phyllis Dan [a], Gennady Rosenblat [b], Saul Yedgar [a,*]

[a] Department of Biochemistry, Hebrew University-Hadassah Medical School, Jerusalem 91120, Israel
[b] Polyol Biotech Ltd, Granot Initiative Center, D.N. Hefer 38100, Israel

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ABSTRACT

Skin inflammatory diseases are most commonly treated with corticosteroids, especially topical preparations, benefitting from high potency and unparalleled formulation flexibility. However, these benefits are limited due to side effects, especially under long-term use. Non-steroidal anti-inflammatory drugs (NSAIDs) which block the COX pathways have been used as safer alternatives to corticosteroids, and much effort and resources have been invested in developing COX inhibitors. However, synthetic NSAIDs are less potent than steroids, have limited formulation flexibility and have their own safety issues, thereby yielding unsatisfactory results, with some high-profile drugs (e.g., the COX-2 inhibitors Vioxx®, Celebrex®) being withdrawn from the market due to safety concerns. The potency and safety challenges of NSAIDs are related to inter-eicosanoid dynamics, pertaining to their pro-versus anti-inflammatory action, homeostatic functions and tissue-specific activities. Instead, the upstream control of phospholipase A2 (PLA2) enzymatic activity, which hydrolyzes cell membrane phospholipids to initiate the eicosanoid production, has been considered for inhibiting eicosanoid activation while maintaining the intricate balance needed for their homeostatic functions. Yet, PLA_2 inhibitors have hardly been tested for treating skin inflammatory/allergic conditions. In this article we review the involvement of PLA_2s in skin physiology and pathology, and discuss the prospect of PLA_2 inhibition for the treatment of dermatological diseases.

Contents

1. Introduction

PLA_2 is a super-family of enzymes catalyzing the hydrolysis of the sn-2 acyl bond of phospholipids (PL) to produce lyso-phospholipids

☆ All authors contributed equally.

* Corresponding author. Tel.: +972 2 643 9218; fax: +972 675 7379.
E-mail address: yedgar@md.huji.ac.il (S. Yedgar).

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(LysoPL) and free fatty acids (FFA), arachidonic acid in particular (Burke and Dennis, 2009a), as illustrated in Fig. 1. This initiates the production of numerous metabolites that mediate diverse pathological conditions, especially inflammatory and allergic diseases. LysoPLs induce activation and extravasation of leukocytes (Rizza et al., 1999). Lyso-phosphatidylserine in particular activates histamine secretion by mast cells (Lloret and Moreno, 1995). LysoPL may induce tissue damage, such as gastric ulceration (Chang et al., 1987), act as a growth factor (especially lyso-phosphatidic acid) and induce proliferation of cancer cells (Goetzl et al., 1999) and tumor metastasis (Fang et al., 2000). LysoPL are also the precursors of PAF, a potent mediator of inflammatory processes (Liu and Xia, 2006).

Arachidonic acid is metabolized by a number of enzymatic pathways to produce numerous lipid products, depicted in Fig. 2, which are involved in the control of many physiological processes and in the induction/propagation of pathological processes, especially inflammatory/allergic processes (Rola-Pleszczynski et al., 1993; Murakami, 2011a). These enzymatic pathways include the cyclooxygenase (COX), lipoxygenase (LOX) and cytochrome P450 (CYP) pathways, which act concertedly to produce prostaglandins and thromboxanes (via COX), leucotrienes, hydroxyeicosatetraenoic acids (HETE) and lipoxines (via LOX), as well as epoxides dihydroxyeicosatetraenoic acid (DiHETE) and HETE (via CYP).

In addition to their lipolytic activity, some PLA_2s act as receptor ligands to activate cell signaling and subsequent proliferation of normal and cancer cells (Kundu and Mukherjee, 1997). Accordingly, the control of PLA_2 has been considered as a therapeutic strategy in the treatment of numerous pathologies, as described in previous reviews (Yedgar et al., 2006; Burke and Dennis, 2009b), but not for skin diseases. The present review is aimed at bridging this gap by reviewing and discussing the role of PLA_2s in skin physiology and in dermatological conditions, and the possibility of targeting them for the treatment of skin inflammatory/allergic diseases.

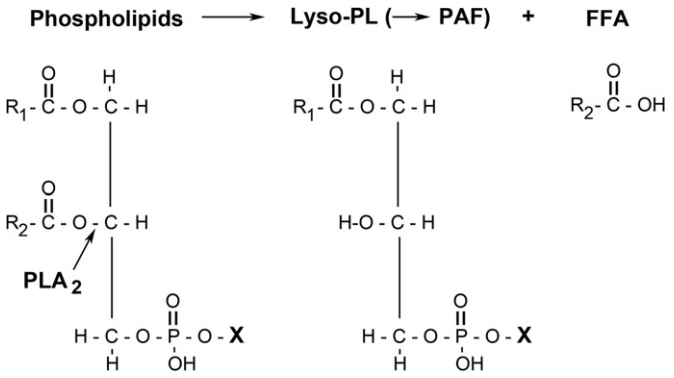

Fig. 1. Phospholipid hydrolysis by phospholipase A_2 (PLA_2) into lyso-phospholipids (Lyso-PL) and free fatty acids (FFA). X stands for: choline (phosphatidylcholine, PC); ethanolamine (phosphatidylethanolamine, PE); serine (phosphatidylserine, PS); inositol (phosphatidylinositol, PI), hydrogen (phosphatidic acid, PA). Lyso-PL is precursor of platelet activating factor (PAF).

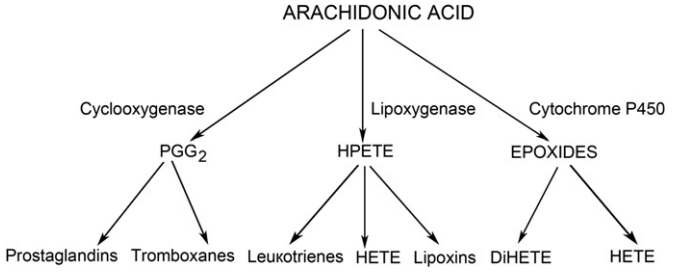

Fig. 2. Metabolism of arachidonic acid into eicosanoid families: PGG_2 = prostaglandin G_2; HPETE = hydroperoxyeicosatetraenoic acid; HETE = hydroxyeicosatetraenoic acids; DiHETE = dihydroxyeicosatetraenoic acid.

2. PLA_2 super-family categories

The PLA_2 enzymes are categorized into different classes according to cellular localization, molecular weight, disulfide bond pattern, calcium-dependence, sequence, and pH of activity. The secreted, cytosolic and Ca-independent PLA_2s ($sPLA_2$, $cPLA_2$, $iPLA_2$ respectively) will be the focus of the present review. In addition, there are the PAF-acetyl hydrolases (PAF-H), hydrolyzing specifically PAF to produce Lyso-PAF, and the lysosomal PLA_2, involved in lipid degradation in acidic lysosomes (Burke and Dennis, 2009b).

2.1. Secretory PLA_2

The secretory PLA_2s ($sPLA_2$) are a low MW (average 14 kD) group of enzymes characterized by at least 6 disulfide bonds, absolute requirement for histidine in the active site, and dependence on mM concentration of calcium. There are 16 different types of $sPLA_2$ numbered (IA-XIV) according to source and disulfide bond pattern. $sPLA_2$ expression has been found in reproductive organs, gestational tissues, skeletal muscle, heart, liver, kidney, thymus, spleen, retina, and skin (Lambeau and Gelb, 2008). $sPLA_2$s are involved in numerous disease states, especially those involving inflammatory/allergic processes such as inflammatory bowel diseases, asthma, arthritis, central nervous system inflammation, pancreatitis, atherosclerosis, cancer and others (Yedgar et al., 2006; Brueseke and Bell, 2006; Hanasaki and Arita, 2002; Lee et al., 2006; Boilard et al., 2003). In general, sPLA2s are involved mainly in the pathophysiology of inflammatory diseases, and have long been considered the "inflammatory enzymes" (Huwiler et al., 1997; Yedgar et al., 2000), but some sPLA2 isoforms have been reported to also have a protective, anti-inflammatory potential (Murakami et al., 2011b). The most well-established physiological role of $sPLA_2$ is as an antimicrobial agent (Buckland and Wilton, 2000; Beers et al., 2002; Murakami et al., 2011b). Group IB $sPLA_2$, known as the pancreatic enzyme, was identified in pancreatic secretions entering the gastrointestinal track (Seilhamer et al., 1986; Puijk et al., 1977; Verheij et al., 1981). However, its role in digestion is ambiguous, as it can be replaced by other enzymes (Valentin et al., 1999; Takemori et al., 1998).

2.2. Cytosolic PLA_2

The cytosolic PLA_2s ($cPLA_2$), consisting of four isoenzymes (Groups IVA–IVD), are larger than the $sPLA_2$s (61–114 kD) with a different pattern of disulfide bonds. Their active site contains a serine/aspartic acid and require μM Ca^{2+} for activity. Group IVA exhibits specificity to phospholipids that contain arachidonic acid at the sn2 position, while Group IVB and Group IVC show no specificity, and Group IVD has preference for linoleic acid (Burke and Dennis, 2009a). $cPLA_2$ has been shown to have both homeostatic roles as well as to be involved in various pathological conditions such as artherosclerosis (Li and Cathcart, 1997; Huber et al., 2006) and neurodegeneration (Kiaei et al., 2005; Kalyvas and David, 2004; Lukiw and Bazan, 2000). $cPLA_2$ levels have been found to fluctuate during the cell cycle (Boonstra and Van Rossum, 2003) and play a role in the female reproductive system (Bonventre et al., 1997).

2.3. Ca-independent PLA_2s

The Ca-independent PLA_2s ($iPLA_2$) consist of six enzymes (Group VI PLA_2) (Akiba and Sato, 2004) that function through a