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Invited review article

Secreted phospholipase A_2 and mast cells

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AA, arachidonic acid; PG, prostaglandin; PLA_2, phospholipase A_2; MC, mast cell; BMMC, bone marrow-derived MC; $bvPLA_2$, bee venom PLA_2; COX, cyclooxygenase; CTMC, connective-tissue MC; $cPLA_2$, cytosolic PLA_2; HDC, histidine decarboxylase; H-PGDS, hematopoietic PGD_2 synthase; $iPLA_2$, Ca^{2+}-independent PLA_2; 5-LOX, 5-lipoxygenase; L-PGDS, lipocalin-type PGD_2 synthase; LT, leukotriene; MMCs, mucosal MC; mPGES-1, microsomal PGE_2 synthase; $sPLA_2$, secreted PLA_2; SCF, stem cell factor

ABSTRACT

Phospholipase A_2s (PLA_2s) are a group of enzymes that hydrolyze the *sn*-2 position of phospholipids to release (typically unsaturated) fatty acids and lysophospholipids, which serve as precursors for a variety of bioactive lipid mediators. Among the PLA_2 superfamily, secreted PLA_2 ($sPLA_2$) enzymes comprise the largest subfamily that includes 11 isoforms with a conserved His–Asp catalytic dyad. Individual $sPLA_2$ enzymes exhibit unique tissue and cellular localizations and specific enzymatic properties, suggesting their distinct biological roles. Recent studies using transgenic and knockout mice for individual $sPLA_2$ isofoms have revealed their involvement in various pathophysiological events. Here, we overview the current state of knowledge about $sPLA_2$s, specifically their roles in mast cells (MCs) in the context of allergology. In particular, we highlight group III $sPLA_2$ (PLA2G3) as an "anaphylactic $sPLA_2$" that promotes MC maturation and thereby anaphylaxis through a previously unrecognized lipid-orchestrated circuit.

Introduction

The mammalian genome encodes more than 30 phospholipase A_2s (PLA_2s) or related enzymes, which are classified into several structurally related families including the intracellular cytosolic PLA_2 ($cPLA_2$) and Ca^{2+}-independent PLA_2 ($iPLA_2$) families and the secreted PLA_2 ($sPLA_2$) family. The $sPLA_2$ family typically consists of low molecular mass, Ca^{2+}-requiring enzymes bearing a His–Asp catalytic dyad. Classically, $sPLA_2$s have been found abundantly in snake or insect venom. In mammals, there are 11 $sPLA_2$s (IB, IIA, IIC, IID, IIE, IIF, III, V, X, XIIA and XIIB), which are subdivided into a conventional group (I, II, V and X) and two atypical groups (III and XII).[1,2] Individual $sPLA_2$s have distinct substrate specificities and tissue distributions, suggesting their distinct, non-redundant roles. Indeed, recent studies using $sPLA_2$ transgenic or knockout mice have revealed that individual $sPLA_2$s exert their specific functions by producing lipid mediators, by altering the composition of membrane phospholipids, by degrading foreign phospholipids in microorganisms or dietary components, or by modifying extracellular non-cellular lipid components (lipoproteins, lung surfactant or microvesicles) in response to given microenvironmental cues. Current understanding of the *in vivo* functions of $sPLA_2$s has been summarized in recent reviews.[1–5] Here, we will make an overview of the biological roles of $sPLA_2$s and the underlying lipid pathways in allergy, focusing on mast cells (MCs) which occupy a central role in allergic responses.

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Regulation of eicosanoid generation by cPLA$_2\alpha$ in MCs

Crosslinking of the high-affinity IgE receptor FcεRI on MCs with IgE and antigen initiates signals leading to the release of allergic mediators that induce immediate hypersensitivity.[3] MCs produce prostaglandin (PG) D_2 and leukotrienes (LTs) B_4 and C_4 as lipid mediators, with preferential production of PGD_2 by connective-tissue MCs (CTMCs) and LTs by mucosal MCs (MMCs). IL-3-driven bone marrow-derived MCs (BMMCs), a relatively immature MC population, produce LTC_4 in preference to PGD_2, thus resembling MMCs. The roles of these eicosanoids in allergy are well documented by other reviews (see reviews by Kabashima and Yokomizo) in this journal issue.

Numerous studies have demonstrated that cPLA$_2\alpha$, which translocates from the cytosol to perinuclear membranes in response to an increase in cytosolic Ca^{2+} and is phosphorylated and activated by mitogen-activated protein kinases, is essential for the stimulus-coupled release of arachidonic acid (AA) from phospholipids and thereby production of eicosanoids in many cell types including MCs.[4,5] Indeed, mice lacking cPLA$_2\alpha$ (*Pla2g4a*$^{-/-}$) or those treated with a cPLA$_2\alpha$ inhibitor show attenuated asthmatic responses upon pulmonary antigen challenge,[6–8] and BMMCs from *Pla2g4a*$^{-/-}$ mice show impaired production of PGD_2, LTs and platelet-activating factor, a lysophospholipid-derived lipid mediator that also participates in allergic responses.[9,10]

Studies using IL-3-driven BMMCs as a model system have revealed that eicosanoid generation by MCs occurs in multiple phases. The immediate response, which occurs within a few minutes, involves explosive activation of cPLA$_2\alpha$ followed by prompt conversion of AA to PGH_2 and then to PGD_2 through the sequential action of cyclooxygenase (COX)-1 and hematopoietic PGD_2 synthase (H-PGDS) and to LTA_4 and then to LTC_4 through that of 5-lipoxygenase (5-LOX) in cooperation with 5-LOX-activating protein and LTC_4 synthase[11] (Fig. 1). The delayed response, which proceeds over several hours, depends entirely on sustained activation of cPLA$_2\alpha$ coupled with *de novo* induction of COX-2.[10,12,13] In a third (or priming) phase, culture of BMMCs with stem cell factor (SCF; a ligand for c-Kit) in the presence of accessory cytokines (*e.g.* IL-3, IL-4, IL-9 and IL-10) for several days not only facilitates MC proliferation, but also partially supports MC maturation toward a PGD_2-producing CTMC-like phenotype through increased expression of cPLA$_2\alpha$, COX-1 and H-PGDS.[14] On the other hand, IL-3 increases the expression of cPLA$_2\alpha$, 5-LOX and LTC_4 synthase, allowing MCs to exhibit a LTC_4-producing MMC-like phenotype.[15] Whereas LTs produced by MCs are pro-allergic,[16] PGD_2 produced by H-PGDS in MCs exhibits anti-allergic rather than pro-allergic effects in anaphylaxis and contact hypersensitivity.[17,18]

Compared to culture with SCF alone, coculture of BMMCs with fibroblasts in the presence of SCF facilitates more efficient maturation toward a CTMC-like phenotype in terms of the appearance of mature granules with greater amounts of histamine and proteases, higher cell surface expression of FcεRI, and the eicosanoid balance shift from LTs to PGD_2.[17,19,20] The latter process is characterized by increased expression of cPLA$_2\alpha$, COX-2 and H-PGDS as well as LTB_4 dehydrogenase, an enzyme that inactivates LTB_4, and decreased expression of LTA_4 hydrolase (LTB_4 synthase) and LTC_4 synthase.[21] During the BMMC-fibroblast coculture, PGE_2, which exerts an anti-allergic effect via the PGE_2 receptor EP3,[22–26] is produced by fibroblasts in a manner dependent upon cPLA$_2\alpha$ in BMMCs, where cPLA$_2\alpha$ -driven AA is transferred to adjacent fibroblasts through the transcellular route and then metabolized to PGE_2 by micosomal PGE_2 synthase (mPGES-1).[23] Mice null for mPGES-1 (*Ptges*$^{-/-}$) or EP3 (*Ptger3*$^{-/-}$) display more severe allergic responses.[22–26] Paradoxically, PGE_2-EP3 signaling induces inflammatory swelling by directly activating MCs.[27] Therefore, the anti-allergic action of PGE_2 may rely on EP3 signaling in stromal cells rather than in MCs.

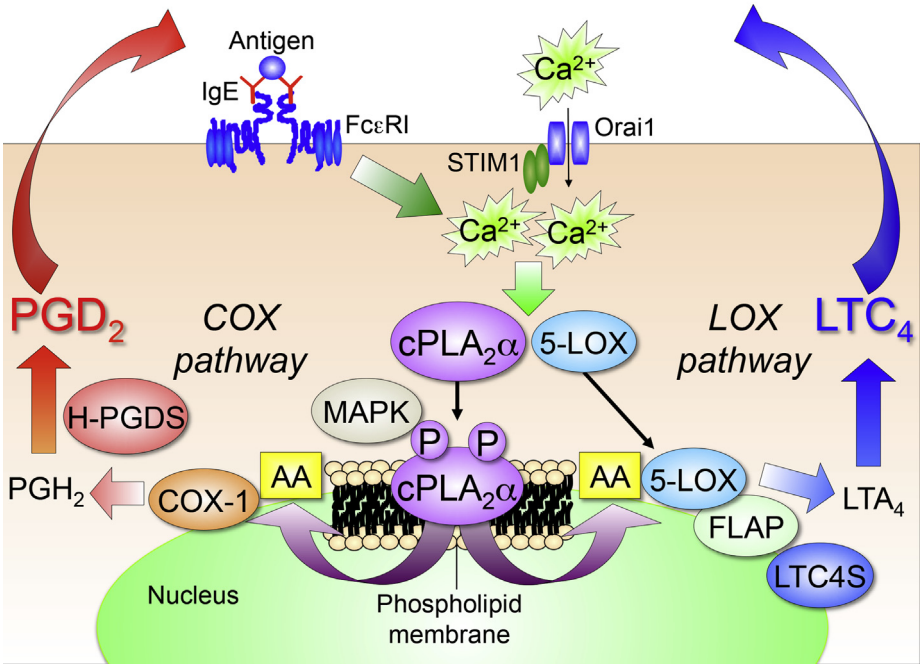

Fig. 1. cPLA$_2\alpha$-dependent eicosanoid biosynthesis in MCs. Following FcεRI crosslinking, cPLA$_2\alpha$ translocates from the cytosol to the perinuclear (preferentially Golgi) membrane in response to Stim1/Orai1-mediated Ca^{2+} influx and is phosphorylated by mitogen-activated protein kinase (MAPK) for optimal activation. The AA released from membrane phospholipids by cPLA$_2\alpha$ is then converted to PGD_2 by the sequential action of cyclooxygenase (COX)-1 (or COX-2 when the cells are primed by particular stimuli) and hematopoietic PGD_2 synthase (H-PGDS) to PGD_2 or by the sequential action of 5-lipoxygenase (5-LOX) in corporation with 5-LOX-activating protein (FLAP) and LTC_4 synthase (LTC4S) to LTC_4.