



Positive and negative roles of lipids in mast cells and allergic responses

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Mast cells are a central immune cell population that are crucial in allergic responses. They secrete granule contents and cytokines and produce a panel of lipid mediators in response to FcεRI-dependent or independent stimuli. Leukotrienes and prostaglandins derived from ω6 arachidonic acid, or specialized pro-resolving lipid mediators derived from ω3 eicosapentaenoic and docosahexaenoic acids, exert pleiotropic effects on various cells in the tissue microenvironment, thereby positively or negatively regulating allergic responses. Mast cells also express the inhibitory receptors CD300a and CD300f, which recognize structural lipids. CD300a or CD300f binding to externalized phosphatidylserine or extracellular ceramides, respectively, inhibits FcεRI-mediated mast cell activation. The inhibitory CD300-lipid axis downregulates IgE-driven, mast cell-dependent type I hypersensitivity through different mechanisms. Herein, we provide an overview of our current understanding of the biological roles of lipids in mast cell-dependent allergic responses.

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Introduction

Lipids play fundamental roles in life as they are essential components of cell membranes, are involved in the body's protective skin barrier, and are a major source

of energy. There are also bioactive lipids that transmit intracellular and intercellular signals, regulating various biological processes including allergic responses and related diseases. Allergies have become very common in more economically developed countries, with a prevalence that has increased by 2–3-fold within the last two decades. Patients with allergic diseases, such as anaphylaxis, asthma, food allergy, allergic rhinitis, and atopic eczema, typically have elevated levels of serum IgE in association with activation of mast cells, a tissue-resident immune cell population whose development in extravascular tissues depends on the stromal cytokine stem cell factor (SCF) and its receptor c-Kit. FcεRI, a high affinity IgE receptor that is expressed on the surface of mast cells, is a tetramer composed of an IgE-binding α chain, a β chain, and two disulfide-linked γ chains. Crosslinking of FcεRI with IgE and allergens, which induces the phosphorylation of an immunoreceptor tyrosine-based activating motif (ITAM) within β and γ chains by activated Src family protein tyrosine kinases (e.g. Lyn), or exposure to several IgE-independent stimuli, triggers exocytosis of granule contents, such as histamine and proteases, as well as secretion of various cytokines and chemokines, thereby promoting allergic inflammation and also regulating host defense against invading microorganisms or venom components. Additionally, mast cells generate a variety of bioactive lipids called 'lipid mediators', which contribute to the fine-tuning of allergic responses by regulating the functions of various cell types. Furthermore, maturation and activation of mast cells are positively or negatively affected by various microenvironmental factors, including lipids. Indeed, lipid-sensing mast cell inhibitory receptors negatively regulate FcεRI signaling to prevent excessive immediate allergic reactions [1].

Herein, we provide an overview of recent topics on the regulatory roles of lipids in allergic responses, with a specific focus on (i) pro-allergic and anti-allergic functions of lipid mediators produced by mast cells or their microenvironments and (ii) the negative regulation of mast cell activation by structural lipids via the CD300 immunoreceptor family.

New insights into the roles of lipid mediators in allergic responses

Lipid mediators are a group of bioactive lipids that are produced spatiotemporally by specific biosynthetic enzymes, act on specific receptors, and are rapidly inactivated enzymatically or non-enzymatically within local tissue microenvironments. Lipid mediators are

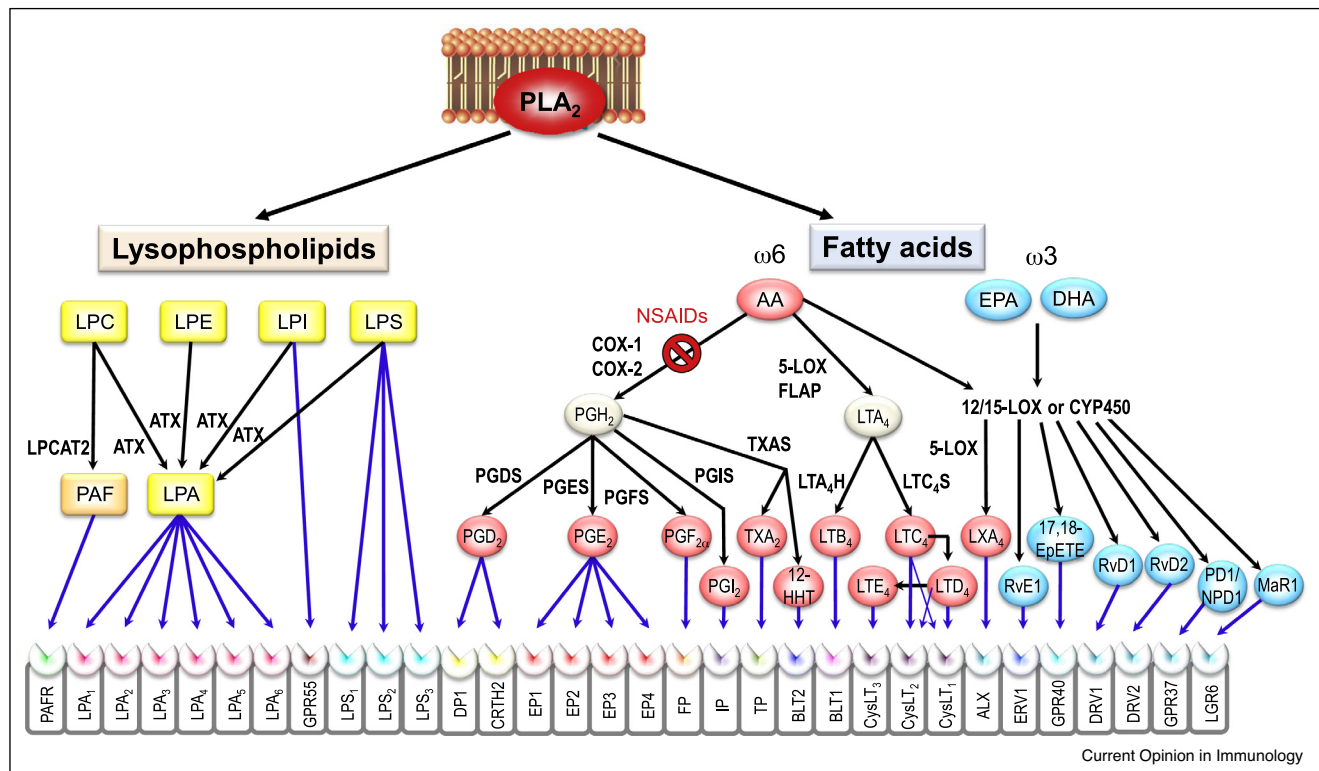
categorized into several classes, including eicosanoids derived from $\omega 6$ arachidonic acid (AA), such as prostaglandins (PGs) and leukotrienes (LTs); specialized pro-resolving lipid mediators (SPMs) derived from $\omega 3$ eicosapentaenoic acid (EPA) or docosahexaenoic acid (DHA), such as resolvins and protectin; and lysophospholipid-derived mediators, such as lysophosphatidic acid (LPA) and platelet-activating factor (PAF). Lipid mediators have pleiotropic functions depending on the context of pathophysiological events, and even a single lipid mediator can exert both offensive and protective effects by acting on distinct receptor subtypes expressed in different cell types [2,3]. Biosynthesis of these lipid mediators is initiated mainly by the hydrolysis of membrane phospholipids by phospholipase A₂s (PLA₂s). Among a number of PLA₂ enzymes identified to date, the release of AA in mast cells is predominantly controlled by group IVA cytosolic PLA₂ (cPLA₂ α), which is translocated from the cytosol to the perinuclear membrane in response to an increase in intracellular Ca²⁺ and is activated by mitogen-activated protein kinases [4]. Mechanistically, the C2 domain of cPLA₂ α binds to phospholipid membranes in the presence of μ M range of Ca²⁺. However, accumulating evidence suggests that various PLA₂s other than cPLA₂ α can also participate in lipid mediator generation by releasing various fatty acids and lysophospholipids in distinct biological settings [5]. The biosynthetic pathways and receptors for these lipid mediators are illustrated in Figure 1.

AA-derived leukotrienes (LTs) are critical mediators of allergic responses. LTB₄ is a potent chemoattractant for leukocytes, while cysteinyl LTs (cysLTs; including LTC₄, LTD₄, and LTE₄) promote sustained smooth muscle contraction, microvascular permeability, and mucus secretion. LTC₄, a main eicosanoid produced by activated mast cells as well as basophils and eosinophils, is synthesized from AA by the sequential action of 5-lipoxygenase (5-LOX) (with 5-LOX-activating protein (FLAP) as a co-factor) and LTC₄ synthase (LTC₄S) and processed to LTD₄ and then to LTE₄ by extracellular peptidases. Among the three cysLT receptors (CysLT₁₋₃), CysLT₁ binds to LTD₄ > LTC₄ > LTE₄, CysLT₂ to LTC₄ = LTD₄ > LTE₄, and CysLT₃ (GPR99) to LTE₄ as determined in heterologous expression systems, although the biology in primary cells is less clear. Genetic deletion of these biosynthetic enzymes or receptors markedly alleviates allergic responses in mice, and CysLT₁ antagonists such as montelukast are now in clinical use for treating patients with asthma [6^{••}]. Not only are they produced by mast cells, but cysLTs (particularly LTE₄) can also drive mast cell activation to induce contractile prostanoid production as downstream effectors through a mechanism involving the montelukast-sensitive CysLT₁ receptor [7]. Recently, cysLTs have attracted attention as potent regulators of group 2 innate lymphoid cells (ILC2s) and thereby type 2 immunity. LTC₄ and LTD₄ induce

CysLT₁-dependent production of IL-4, IL-5, and IL-13 by ILC2s in synergy with the epithelial-derived cytokines IL-25 and IL-33, and facilitate the accumulation of ILC2s, Th2 cells, and eosinophils after allergen challenge [8,9]. Additionally, CysLT₂-dependent production of IL-33 by type 2 alveolar epithelial cells leads to expansion of IL-5/IL-13-producing ILC2s, and pharmacological blockade of CysLT₂ mitigates IL-33-dependent mast cell activation and lung pathology [10]. Inhalation of an allergen leads to the expansion of IL-25-producing airway brush cells, which is attenuated by genetic deletion of LTC₄S or CysLT₃. LTE₄ inhalation is sufficient to elicit CysLT₃-dependent brush cell expansion, indicating that the LTE₄-CysLT₃ axis regulates the expansion of IL-25-producing airway brush cells leading to type 2 immune responses [11[•]]. Similar to airway brush cells, intestinal tuft cells produce cysLTs that cooperate with IL-25 to activate ILC2s, and tuft cell-specific ablation of cysLT synthesis attenuates type 2 immunity against helminth infection or food allergens [12^{••},13]. In addition to the action of cysLTs on ILC2s, mast cell-derived LTC₄ and sphingosine-1-phosphate (S1P), a sphingolipid-derived lipid mediator, act on CysLT₂ and S1P₁ receptors, respectively, on natriuretic polypeptide-positive (Nppb⁺) sensory neurons to elicit itch [14[•]], underscoring a novel mechanism for mast cell-induced itch.

PGD₂ is another major AA-derived eicosanoid produced by activated mast cells. PGD₂ is synthesized from AA by the sequential action of cyclooxygenases (COX-1 or 2) and terminal PGD₂ synthases [hematopoietic (H-) or lipocalin-type (L-) PGDSs] and acts on two types of PGD₂ receptors (DP1 and DP2, the latter more generally known as CRTH2) on target cells. PGD₂ exerts pro-allergic and anti-allergic functions depending on the disease context. Global deficiency of DP1 ameliorates asthma and anaphylaxis [15], which may be attributed in part to impaired maturation of mast cells [16^{••}]. PGD₂ produced by L-PGDS in neighboring fibroblasts is selectively coupled with DP1-driven mast cell maturation, while group III PLA₂ (PLA2G3) secreted from mast cells lies upstream of fibroblastic L-PGDS, revealing the PLA2G3-L-PGDS-DP1 paracrine loop toward proper maturation of mast cells [16^{••}]. In contrast, DP1 deficiency increases the migration of antigen-captured dendritic cells to the lymph nodes, exacerbating contact hypersensitivity [17]. Global or mast cell-specific deletion of H-PGDS worsens anaphylaxis [16^{••}] and food allergies with mast cell hyperplasia [18]. The anti-inflammatory action of PGD₂ can be accounted for, at least in part, by its non-enzymatic conversion to 15-deoxy-PGJ₂, an anti-inflammatory eicosanoid that acts on the nuclear receptor PPAR γ to dampen pro-inflammatory NF- κ B signaling [19]. As in the case of cysLTs, PGD₂ has been implicated in ILC2 regulation. Mast cell-derived PGD₂ is critical for ILC2 expansion via CRTH2 [20]. CRTH2-deficient mice exhibit reduced pulmonary ILC2 responses and type

Figure 1



Biosynthetic pathways for various lipid mediators from membrane phospholipids.

PLA₂ enzymes hydrolyze membrane phospholipids to liberate lysophospholipids and fatty acids. The lysophospholipids lysophosphatidylcholine (LPC), lysophosphatidylethanolamine (LPE), lysophosphatidylinositol (LPI), and lysophosphatidylserine (LPS) are converted to LPA by autotaxin (ATX), and alkyl-LPC is converted to PAF by LPC acyltransferase 2 (LPCAT2). ω6 AA is converted to PGH₂, an intermediate PG, by COX-1 or 2, and then metabolized to bioactive prostanoids, including PGD₂, PGE₂, PGF_{2α}, PGI₂, thromboxane A₂ (TXA₂), and 12(S)-hydroxyheptadecatrienoic acid (12-HHT), by the respective synthases. PG biosynthesis is blunted by non-steroidal anti-inflammatory drugs (NSAIDs, such as aspirin), which inhibit constitutive COX-1 and inducible COX-2. AA is also converted to LTA₄, an intermediate LT, by 5-LOX with FLAP as a co-factor, after which it is metabolized to LTB₄ by LTA₄ hydrolase (LTA₄H) or conjugated with glutathione to give rise to LTC₄ by LTC₄S. LTC₄ is sequentially converted to LTD₄ and then to LTE₄. AA is also converted to lipoxin A₄ (LXA₄) by a combined action of 12/15-LOX and 5-LOX. ω3 EPA and DHA are converted by 12/15-LOX or CYP450 enzymes to various SPMs, including ω3 epoxides (e.g. 17,18-EpETE), resolvins (e.g. RvE1, RvD1 and RvD2), protectins (e.g. PD1/NPD1), and maresins (e.g. MaR1). These lipid mediators act on their cognate G protein-coupled receptors to induce specific cellular responses. For details, please see the text.

2 inflammation, which are rescued by adoptive transfer of CRTH2-sufficient ILC2s [21]. LTE₄ potentiates the ability of PGD₂ to induce ILC2 and Th2 cells [22,23^{*}], implying a synergistic action of the two mast cell-derived eicosanoids in facilitating type 2 immunity. Moreover, PGD₂ produced by ILC2s and effector Th2 cells, both of which express the PGD₂ synthase H-PGDS and the PGD₂ receptor CRTH2 in response to IL-25, IL-33, or TSLP, is crucial for autocrine activation of these cells, leading to eosinophilic inflammation [24,25].

Although mast cells produce minimal PGE₂, this pleiotropic AA-derived eicosanoid is supplied from the micro-environment and plays an anti-allergic role in most cases by acting on four types of EP receptors (EP1–4). Genetic deletion of EP3 leads to exacerbation of asthma, skin hypersensitivity, and anaphylaxis [26–28], although it

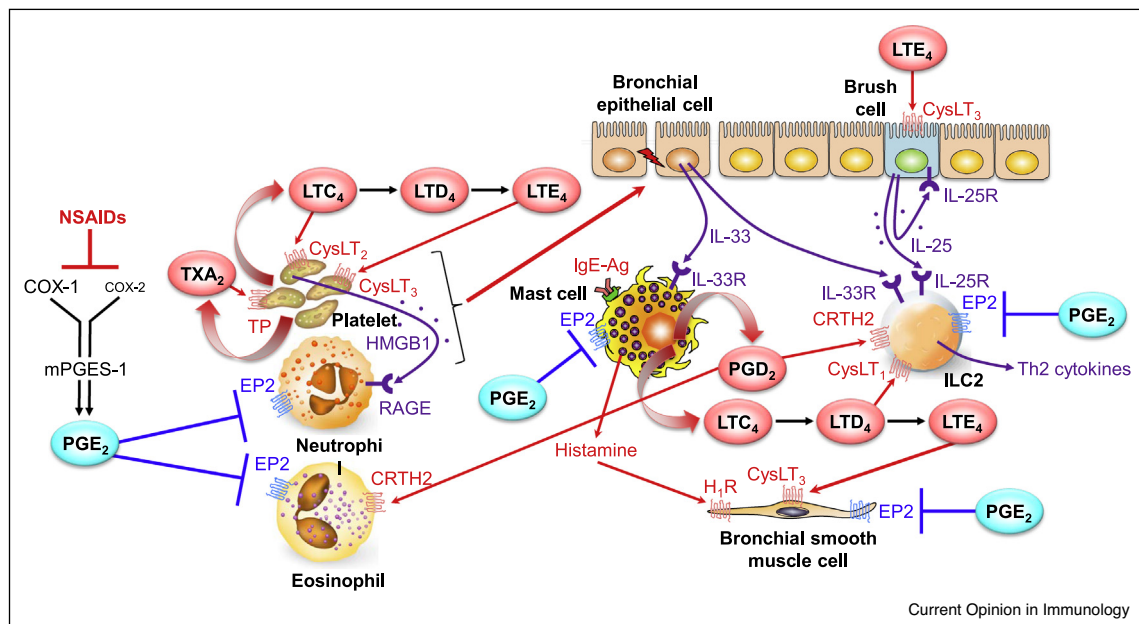
paradoxically facilitates the activation and chemotaxis of mast cells [29,30]. Aspirin-exacerbated respiratory disease (AERD) is characterized by asthma, eosinophilia, overproduction of cysLTs, bronchoconstriction, mucus secretion, and mast cell activation to COX inhibitors. Deficiency of PGE₂ synthase (mPGES-1) or inhibition of COX-1 rather than COX-2 causes an AERD-like phenotype that depends on platelets and cysLTs, an event that is reversed by treatment with EP2 and to a lesser extent EP1 agonists [31^{*}]. Aspirin-induced cysLT generation and mast cell activation depend on the adherent interaction of platelets with granulocytes and thromboxane receptor (TP) signaling [32]. Thus, lesions that impair the inducible generation of PGE₂ disturb the adequate control of platelet-granulocyte interactions and TP-dependent cysLT production, permitting mast cell activation in response to COX-1 inhibition. Additionally,

PGE₂-EP2 signaling suppresses mast cell activation [33], promotes vascular remodeling [34], attenuates eosinophilia [35], prevents proliferation of ILC2s and Th2 cells [36,37], and negatively regulates atopic dermatitis-like inflammation by suppressing TSLP expression [38]. This eicosanoid network in allergic responses, as described above, is summarized in Figure 2.

ω 3 EPA and DHA are converted by 12/15-LOX and/or cytochrome P450 (CYP450) enzymes, as well as by acetylated COX-2 in the presence of aspirin, to SPMs with potent anti-inflammatory and/or pro-resolving functions. Individual SPMs act on specific receptors such as ERV1/ChemR23 for resolvin E1 (RvE1), DRV1/GPR32 for resolvin D1 (RvD1), DRV2/GPR18 for resolvin D2 (RvD2), and GPR37 for protectin D1 (PD1, also known as neuroprotectin D1 (NPD1)) [39^{••}]. Functionally, these SPMs can limit leukocyte recruitment, induce granulocyte apoptosis, enhance efferocytosis by phagocytes, facilitate the switch from M1 to M2 macrophages, promote the return of non-apoptotic cells to lymphatics and blood vessels, and help initiate tissue repair and healing. By employing comprehensive lipidomics, a new class of ω 3 EPA/DHA-derived epoxy-metabolites (ω 3 epoxides), such as 17,18-epoxyeicosatetraenoic acid (17,18-EpETE)

and 19,20-epoxydocosapentaenoic acid (19,20-EpDPE), was recently found to be constitutively released from mast cells. These unique ω 3 lipid mediators are produced by PAF-AH2 (group VIIB PLA₂), an oxidized phospholipid-selective PLA₂ [40^{••}]. Unlike the canonical route for eicosanoid biosynthesis, in which the AA released by cPLA₂ α from membrane phospholipids is metabolized by downstream enzymes to eicosanoids, ω 3 epoxides are liberated directly by PAF-AH2 from pre-formed ω 3 epoxide-esterified phospholipids (Figure 3). Genetic or pharmacological inactivation of PAF-AH2 reduces the steady-state production of ω 3 epoxides, leading to attenuated mast cell activation and anaphylaxis following Fc ϵ RI crosslinking. Mechanistically, ω 3 epoxides promote IgE-mediated activation of mast cells by downregulating Srcin1, a Src-inhibitory protein that counteracts Fc ϵ RI signaling, through a pathway involving PPAR γ [40^{••}]. Although ω 3 fatty acids are generally believed to have beneficial effects on various biological events, the immunosuppressive action of their metabolites may be disadvantageous to host defense [41]. Conceivably, Fc ϵ RI-dependent mast cell activation may have originally evolved as a defense system against harmful venom, bacteria, and/or parasites [42[•]], where the ω 3 epoxide-mediated optimization of Fc ϵ RI signaling may contribute

Figure 2

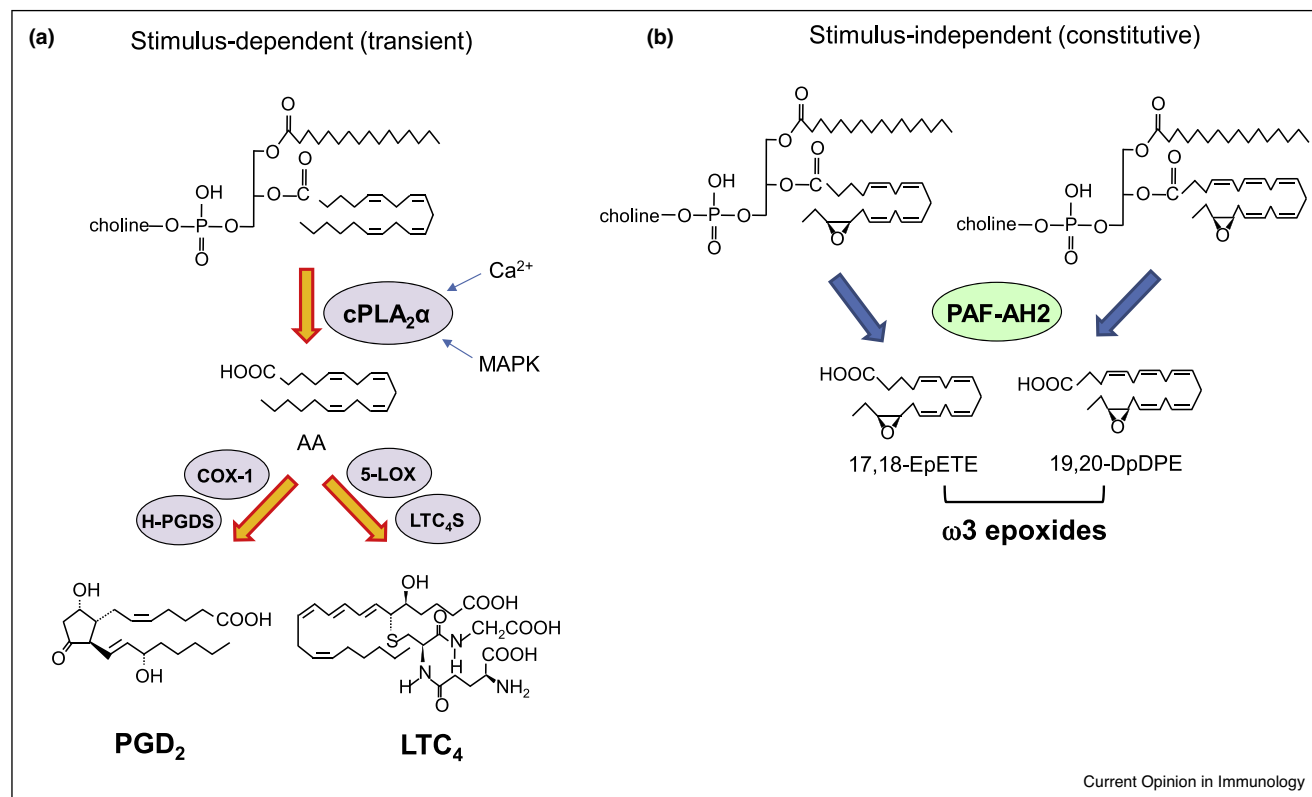


Lipid mediator networks in asthma.

Mast cells activated by IgE and antigen (Ag) or by IL-33 derived from damaged bronchial epithelial cells produce PGD₂ and cysLTs, which act on CRTH2 and CysLT₁, respectively, to enhance ILC2 activation. Mast cell-derived LTE₄ and histamine promote the contraction of bronchial smooth muscle cells. LTE₄ activates brush cells to produce IL-25, which in turn stimulates ILC2-dependent type 2 immunity. PGD₂ promotes eosinophil migration via CRTH2.

Platelets also produce cysLTs, which facilitate the interaction between platelets and neutrophils via CysLT₂ and CysLT₃, leading to the activation of neutrophils that damage bronchial epithelial cells to release IL-33. PGE₂, produced mainly by COX-1 and microsomal PGE₂ synthase (mPGES-1) in the airway microenvironment, attenuates multiple steps of the aforementioned responses via EP2. NSAIDs inhibit COX enzymes to shut down PGE₂ in the airway, thereby exacerbating type 2 inflammation.

Figure 3



Two modes of lipid mediator production by PLA₂s in mast cells.

(a) In response to Ca²⁺ and phosphorylation by mitogen-activated protein kinase (MAPK) following FcεRI-driven mast cell activation, cPLA₂α hydrolyzes PC in the perinuclear membrane to selectively release AA, which is then converted to PGD₂ by COX-1 (or COX-2) and H-PGDS and to LTC₄ by 5-LOX and LTC₄S.

(b) PAF-AH2 constitutively releases ω3 epoxides (17,18-EpETE and 19,20-DpDPE) by directly hydrolyzing ω3 epoxide-esterified PC.

to the maintenance of a healthy state. In a more hygienic environment, however, this protective response has been shifting to deleterious outcomes against exposure to environmental allergens, manifesting as allergic diseases. In contrast, 17,18-EpETE produced from dietary EPA by intestinal microbiota suppresses contact hypersensitivity by inhibiting neutrophil migration by acting on the fatty acid receptor GPR40 [43,44], indicating that the actions of ω3 metabolites are context-dependent.

Negative regulation of mast cell activation by structural lipids via the CD300 immunoreceptor family

The CD300 immunoreceptor family is a group of type I transmembrane receptors with an extracellular immunoglobulin variable region (IgV)-like domain, which regulates immune responses through paired activating and inhibitory functions [45,46]. Both CD300a and CD300f are inhibitory receptors, whereas other CD300 members are activating receptors. CD300a contains two immunoreceptor tyrosine-based inhibitory motifs (ITIMs) in the cytoplasmic region, while CD300f harbors two ITIMs and a single

immunoreceptor tyrosine-based switch motif (ITSM). Both CD300a and CD300f are highly expressed on mast cells [45–50]. Interestingly, their ligands include several types of structural lipids [e.g. phosphatidylserine (PS), phosphatidylethanolamine (PE), ceramides, and sphingomyelin] [51,52^{••},53–59]. These inhibitory receptors recognize PS and/or PE exposed on apoptotic/dead cells, thereby regulating their clearance by phagocytes [57–59].

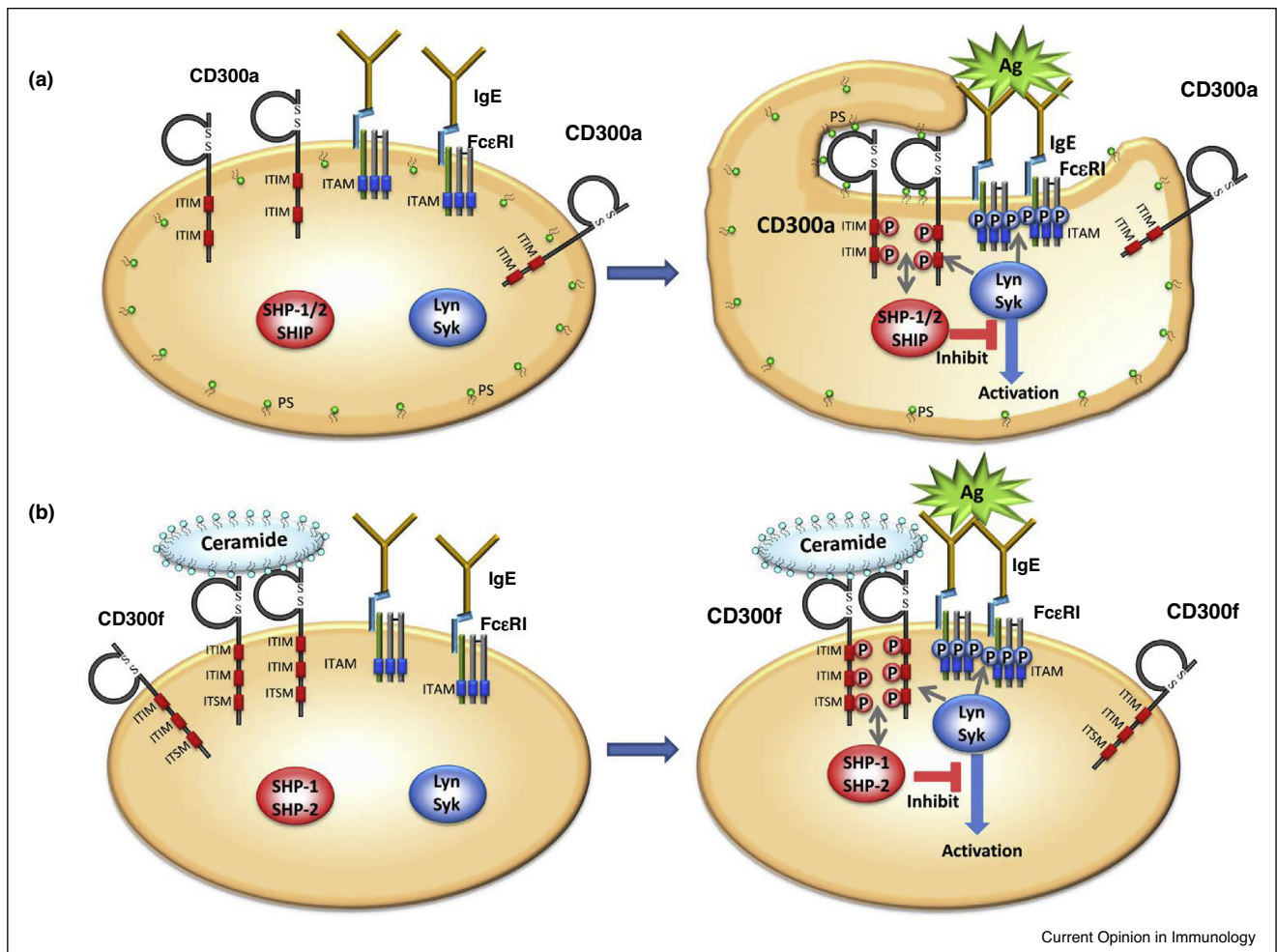
Artificial co-engagement of FcεRI and either CD300a or CD300f with specific antibodies in murine mast cells inhibits FcεRI-mediated mast cell activation [48–50,60–64]. Murine CD300a inhibits FcεRI signaling via phosphorylation of two ITIMs that can recruit SH2-containing protein tyrosine phosphatase 1 (SHP-1), SHP-2, or SH2-containing inositol-5-phosphatase (SHIP) [49,63], while murine CD300f inhibits FcεRI signaling via phosphorylation of two ITIMs and a single ITSM that can recruit SHP-1 and SHP-2 [52^{••},64]. Importantly, IgE/mast cell-dependent passive anaphylactic responses are enhanced in both CD300a-deficient and CD300f-deficient mice [52^{••},65^{••}]. Since CD300a or CD300f deficiency does not affect mast cell differentiation and number in tissues, these results show

that both CD300a and CD300f inhibit IgE-driven mast cell activation *in vivo* [52^{••},65^{••}]. However, CD300a-deficient, but not CD300f-deficient mast cells [52^{••},65^{••}], exhibit enhanced degranulation compared with their wild-type counterparts in response to IgE plus antigen, implying that there are different mechanisms underlying CD300a-mediated and CD300f-mediated inhibition of FcεRI signaling. Following FcεRI crosslinking, PS is externalized on the surface of mast cells, and subsequently co-localized with CD300a on the same surface. The direct *cis*-interaction between CD300a and PS suppresses FcεRI signaling [65^{••}]. Furthermore, pretreatment with anti-CD300a blocking antibody enhances FcεRI-mediated activation of mast cells *in vitro* and *in vivo* [60,65^{••}], consistent with

the observation that CD300a deficiency enhances IgE-driven mast cell activation *in vivo* [65^{••}].

Ceramides emerged as potential ligands for CD300f [52^{••}]. Indeed, the binding of plate-coated ceramides to CD300f suppresses FcεRI-mediated degranulation in BMMC, as shown by *in vitro* analysis of mast cell degranulation where ceramide is not available. Moreover, extracellular ceramides are distributed in the tissues surrounding mast cells, and pretreatment with anti-ceramide antibody disrupts the ceramide-CD300f interaction and augments passive cutaneous anaphylaxis (PCA) responses in wild-type mice. In contrast, pretreatment with ceramide liposomes increase the ligand levels for CD300f *in vivo* and inhibited PCA responses

Figure 4



The inhibitory CD300-lipid axis downregulates FcεRI-mediated mast cell activation through different mechanisms.

(a) Under steady-state conditions, PS is not externalized on the surface of mast cells. The direct *cis*-interaction between CD300a and PS externalized on the surface of mast cells after FcεRI engagement inhibits FcεRI signaling via phosphorylation of ITIMs.

(b) Under steady-state conditions, ceramide-bound CD300f does not co-localize with FcεRI on the surface of mast cells. Only after FcεRI engagement can ceramide-bound CD300f access the aggregated FcεRI. Subsequently, activated tyrosine kinases downstream of FcεRI efficiently phosphorylate ITIMs/ITSM of ceramide-bound CD300f, inhibiting FcεRI signaling.

in wild-type mice. The same pretreatment does not influence PCA responses in CD300f-deficient mice. Thus, the interaction between CD300f and extracellular ceramides inhibits FcεRI signaling *in vivo* [52^{••}]. Interestingly, under steady-state conditions, CD300f, either ceramide-bound or free, does not co-localize with FcεRI on the surface of mast cells. Only after FcεRI engagement does ceramide-bound CD300f access the aggregated FcεRI. Subsequently, activated tyrosine kinases downstream of FcεRI efficiently phosphorylate the ITIM/ITSM of ceramide-bound CD300f, culminating in down-regulation of FcεRI signaling *in vivo* [52^{••}]. CD300f inhibits the development of IgE/mast cell-dependent asthma or food allergies in mouse models [52^{••},66]. In addition to ceramides, human, but not murine, CD300f recognizes sphingomyelin to inhibit FcεRI-mediated mast cell activation [54]. The extracellular IgV-like domain of human CD300f involving lysine (K)-67 [versus murine CD300f involving glutamic acid (E)-68] is pivotal for the recognition of sphingomyelin [67,68].

Overall, both CD300a-PS and CD300f-ceramide interactions impede mast cell activation *in vivo* only after FcεRI engagement (Figure 4) [52^{••},65^{••}]. Notably, the interaction between apoptotic/dead cell-exposed PS and CD300a inhibits TLR4-mediated mast cell activation [56], whereas ceramide-bound CD300f inhibits Mrgprb2/MRGPRX2-mediated, P2X7-mediated, or TLR4-mediated mast cell activation [69–72]. These phenomena may be associated with CD300a-mediated or CD300f-mediated suppression of IgE-independent allergic diseases. To understand the underlying mechanisms, dynamic changes in the level of PS, PE, ceramides, and sphingomyelin on the surface of and in the tissues surrounding mast cells remain to be investigated.

Concluding remarks

In this review, we highlighted recent advances in the biological roles of lipids in allergic responses in association with mast cell biology. Although we have mainly focused on limited types of lipid mediators, including cysLTs, PGD₂, PGE₂, and ω3 epoxides, there are others that have some influence on mast cell functions and thereby allergic pathology. For instance, several lysophospholipid-derived mediators such as SIP, LPA, PAF, and lysoPS have also been implicated in allergic reactions through multiple mechanisms. Besides these lipid mediators, recent studies have identified structural lipids as ligands for inhibitory CD300a and CD300f in mast cells, where the inhibitory CD300-lipid axis acts as a braking system in immediate allergic reactions. Lipid-metabolic pathways are complex, often redundant, and highly interconnected; in some cases, they are counter-regulatory. Although not stated in this review, mast cell activation is also affected by bioenergetics coupled with fatty acid β-oxidation as well as by lipid composition in membrane microdomains, which may have variable impacts on

signaling potency through FcεRI or other receptors. Thus, a full understanding of the lipid network in relation to mast cells and allergic responses should be further elucidated using advanced analytical techniques such as spatiotemporal lipid imaging and untargeted lipidomics. Hopefully, these approaches will allow the therapeutic application of novel agents that target-specific lipid pathways in human diseases.

Conflict of interest statement

Nothing declared.

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