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Sphingosine-1-phosphate and other lipid mediators generated by mast cells as critical players in allergy and mast cell function

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ABSTRACT

Sphingosine-1-phosphate (S1P), platelet activating factor (PAF) and eicosanoids are bioactive lipid mediators abundantly produced by antigen-stimulated mast cells that exert their function mostly through specific cell surface receptors. Although it has long been recognized that some of these bioactive lipids are potent regulators of allergic diseases, their exact contributions to disease pathology have been obscured by the complexity of their mode of action and the regulation of their metabolism. Indeed, the effects of such lipids are usually mediated by multiple receptor subtypes that may differ in their signaling mechanisms and functions. In addition, their actions may be elicited by cell surface receptor-independent mechanisms. Furthermore, these lipids may be converted into metabolites that exhibit different functionalities, adding another layer of complexity to their overall biological responses. In some instances, a second wave of lipid mediator synthesis by both mast cell and non-mast cell sources may occur late during inflammation, bringing about additional roles in the altered environment. New evidence also suggests that bioactive lipids in the local environment can fine-tune mast cell maturation and phenotype, and thus their responsiveness. A better understanding of the subtleties of the spatiotemporal regulation of these lipid mediators, their receptors and functions may aid in the pursuit of pharmacological applications for allergy treatments.

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1. Introduction

Mast cells differentiate in peripheral tissues from myeloid lineage progenitors. Influenced by stem cell factor (SCF) and other signals in

their environment, they acquire their characteristic granularity by storing a variety of substances, including proteases, proteoglycans and vascular mediators in intracellular vesicles (Douaiher et al., 2014; Galli et al., 2005; Metz et al., 2007; Olivera and Rivera, 2014). Concomitantly, they gain cell surface expression of the high affinity receptor for IgE, FcεRI. This allows the mast cell to respond to an antigen by releasing the contents of its granules (degranulation), a critical process for the initiation of the immediate allergic response (Galli and Tsai, 2012; Rivera and Gilfillan, 2006). Antigen-stimulated mast cells also actively produce and secrete a wide variety of lipids and proteins that require *de novo* synthesis (Blank et al., 2014; Galli et al., 2005; Metz et al., 2007). Among the lipid mediators that mast cells abundantly synthesize are eicosanoids (prostaglandins and leukotrienes), platelet activating factor (PAF) and sphingosine-1-phosphate (S1P) (Boyce, 2007; Mencia-Huerta et al., 1983; Olivera, 2008). These mediators are exported from mast cells within minutes after stimulation (eicosanoids and PAF) or at later times (S1P) and act in the surrounding environment by binding to various types of cognate receptors from the G-protein coupled receptor superfamily (GPCR), which are ubiquitously expressed in tissues and cells. These lipid-binding receptors modulate host defense and the allergic immune response, among

Abbreviations: AA, arachidonic acid; ABCC1, ATP-binding cassette, sub-family C; BLT₁₋₂, leukotriene B4 receptors 1 to 2; BMMC, bone marrow derived mast cells; COX, cyclooxygenase; Cys-LT, cysteinyl leukotrienes; CysLT₁₋₂, cysteinyl leukotriene receptors 1–2; DP₁₋₂, prostaglandin D2 receptors 1 to 2; FcεRI, high affinity receptor for IgE; GPCR, G-protein coupled receptor; KIT, stem cell factor receptor; 5-LO, 5-lipoxygenase; LTB₄, leukotriene B4; LTC₄, leukotriene C4; LTC₄S, leukotriene C4 synthase; eNOS, endothelial nitric oxide synthase; NO, nitric oxide; PLA₂, phospholipase A2; PAF, platelet activating factor; PGD₂, prostaglandin D2; PGE₂, prostaglandin E2; PGDS, prostaglandin D synthase; PI3K, phosphatidylinositol-4,5-bisphosphate 3-kinase; SphK, sphingosine kinase; S1P, sphingosine-1-phosphate; S1P₁₋₅, sphingosine-1-phosphate receptors 1 through 5; SCF, stem cell factor; RBL-2H3, basophilic leukemia cell line; TNF, tumor necrosis factor; TRAF2, TNF receptor-associated factor 2

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other biological processes, by affecting vascular permeability and contractility, chemotaxis of immune cells to sites of inflammation and by inducing varied responses in stromal cells (Boyce, 2007; Honda et al., 2002; Rivera et al., 2008; Serhan et al., 2008). Because most of the above mentioned lipid mediators may bind several types of distinct receptors and each receptor is poised to generate unique downstream signals by virtue of their coupling to varied $G\alpha$ subunits, the predominant biological function that results may depend on the population of cells present in the tissue as well as the quantitative and qualitative differences in the receptors engaged. Consequently, engagement of specific lipid mediator receptors may mediate pro-inflammatory functions or contribute to the resolution of inflammation depending on the tissue they act on and the timing of action.

Although cell surface expression of FcεRI and KIT (the receptor for SCF) and high metachromatic granularity are common hallmarks of differentiated mast cells, the granule content, life span and functionality of these cells can vary significantly depending on the surrounding microenvironment (Bankova et al., 2014; Douaiher et al., 2014; Galli et al., 2005). This is partly due to the diversity of cell surface receptors expressed by mast cells that makes them susceptible to unique environmental signals in the niche they occupy. Since mast cells are long-lived tissue residents with slow turnover (Padawer, 1974), mast cell-derived mediators may influence the differentiation of mast cell progenitors as well as the phenotype of mature mast cells throughout the course of an immune response. For example, it has been recently described that in a mouse model for the “atopic march”, exposure to a given allergen may alter mast cell responses to a different allergen later in life by increasing mast cell numbers and modifying their phenotype from an immuno-suppressive to a pro-inflammatory mast cell (Hershko et al., 2012). Mast cells express a repertoire of lipid mediator receptors, and thus, in addition to their direct contribution to allergic disease (pro- or anti-inflammatory), these lipids may influence mast cell responses and mast cell differentiation or phenotype, altering their potential involvement in inflammatory processes. Here we will summarize current knowledge about the production of lipid mediators in mast cells, particularly S1P, and the different aspects of their contribution to allergy.

2. Sphingosine-1-phosphate (S1p)

Sphingosine-1-phosphate (S1P) is a bioactive sphingolipid metabolite derived from sphingosine, an 18-carbon amino alcohol. Structurally, sphingosine linked to a long fatty acid (ceramide) is the fundamental building block of complex sphingolipids (Hannun and Obeid, 2008). Numerous stimuli can release sphingosine from membrane ceramides, a process catalyzed by cellular ceramidases, and activate one or both sphingosine kinase isoforms (SphK1 and SphK2) that phosphorylate sphingosine to generate S1P intracellularly (Fig. 1) (Olivera, 2008; Taha et al., 2006). S1P thus produced can modulate cellular processes, including those important for inflammation and immune responses, mostly through its G-protein coupled receptors (S1PR₁₋₅) (Hannun and Obeid, 2008; Sanchez and Hla, 2004), a process that requires S1P export from cells by specific transporters. The difference in expression patterns of the five S1P receptors on different cells types confers signaling specificity elicited by the ubiquitous S1P molecule. In addition to its autocrine and/or paracrine mode of action, S1P may also act intracellularly by binding intracellular receptors or targets, adding another layer of complexity and regulation to S1P-mediated signaling (Maceyka and Spiegel, 2014; Olivera, 2008).

A critical aspect for S1P biological functions is that, under homeostatic conditions, there is a sharp differential between the levels of S1P in circulation (micromolar range) and those found in tissues (nanomolar range) (Olivera et al., 2013a; Schwab et al., 2005). The high S1P concentrations in blood and lymph signal immune cells

to migrate out of primary and secondary lymphoid organs (low S1P zones) into circulation (high S1P zones). In addition, the presence of S1P micro-gradients within the tissue can regulate movement of immune cells to and from particular substructures (Arnon and Cyster, 2014; Moriyama et al., 2014). The steep S1P gradient between blood and organs is maintained by enzymatic activities that constantly degrade S1P in tissues (mainly S1P lyase (Schwab et al., 2005; Serra and Saba, 2010) and two specific S1P phosphatases (SPP1 and SPP2) (Olivera et al., 2013a)) (Fig. 1). On the other hand, the major sources of circulating S1P are red blood cells and endothelial cells (Olivera et al., 2013a; Pappu et al., 2007). Aberrant maintenance of S1P gradients can cause lymphopenia, vascular barrier dysfunction, and other abnormalities.

Mast cells, through engagement of FcεRI, KIT or IL-3 receptors (and possibly other receptors) generate and release abundant quantities of S1P. This may cause temporary increases in the levels of S1P in tissues that can effectively engage S1P receptors in surrounding cells and elicit responses (Choi et al., 1996; Jolly et al., 2004; Olivera et al., 2006; Prieschl et al., 1999). Furthermore, mast cell-generated S1P controls critical mast cell effector functions. Genetic deletion or silencing of SphKs results in pronounced deficiencies in both immediate and delayed mast cell responses, including degranulation, cytokine and eicosanoid production and chemotaxis (Dillahunty et al., 2013; Mitra et al., 2006; Olivera et al., 2007). Both isoforms of sphingosine kinase (SphK1 and 2) are activated upon antigen stimulation (Fig. 2) (Dillahunty et al., 2013; Olivera et al., 2006; Oskertizian et al., 2008). However, while SphK1 is key for regulating most human mast cell responses, SphK2 is predominant in most mouse mast cell responses. In addition to the species of origin, the role or predominance of each isoform in particular mast cell functions seems to depend on the tissue of origin and the stage of mast cell differentiation (Dillahunty et al., 2013). We will briefly review the mechanisms of S1P production and release following engagement of FcεRI, and the current view of how mast cell-generated S1P may affect both, mast cell phenotype and function as well as the surrounding microenvironment.

2.1. S1P generation and export by IgE/antigen stimulated mast cells

Upon IgE/antigen-mediated activation of mast cells, FcεRI receptors associate with lipid rafts where sphingolipids are enriched. Activation of FcεRI facilitates the recruitment of both SphK1 and SphK2 to lipid rafts in proximity to their substrate via the Src kinase family members Fyn and, particularly, Lyn (Olivera et al., 2006; Urtz et al., 2004). Fyn and Lyn also provide additional signals for the activation of SphKs. For example, downstream of Fyn, the adaptor protein GRB2-associated-binding protein 2 (Gab2) and PI3K activity are required for maximal activation of SphKs (Olivera et al., 2006). While Fyn deficiency results in a complete loss of SphK activation, Lyn deficiency delays the activation of SphKs (Urtz et al., 2004). As a consequence of Fyn and Lyn activities, a peak in intracellular S1P levels ensues within minutes of FcεRI engagement (Olivera et al., 2006) but this early rise is not accompanied by a detectable release into the extracellular space (Mitra et al., 2006; Olivera, 2008) and it may be linked to its regulation of mast cell responses. A second phase in the production of S1P occurs after 30 min, coinciding with the maximal activity of SphK (Olivera et al., 2006), and precedes its transport out of mast cells and appearance in the extracellular media. Although S1P in the extracellular space has also been detected in low amounts at earlier time points, this was observed after pre-loading mast cells with [3H]-Sphingosine (Mitra et al., 2006), which itself may alter this response.

Efficient transport of charged S1P molecules across cellular membranes requires active export by specific transporters. A recently identified bona-fide transporter for S1P is a member of the major facilitator superfamily (MFS), Spns2. Its role in S1P export has been demonstrated in zebrafish and in mice with a major impact on

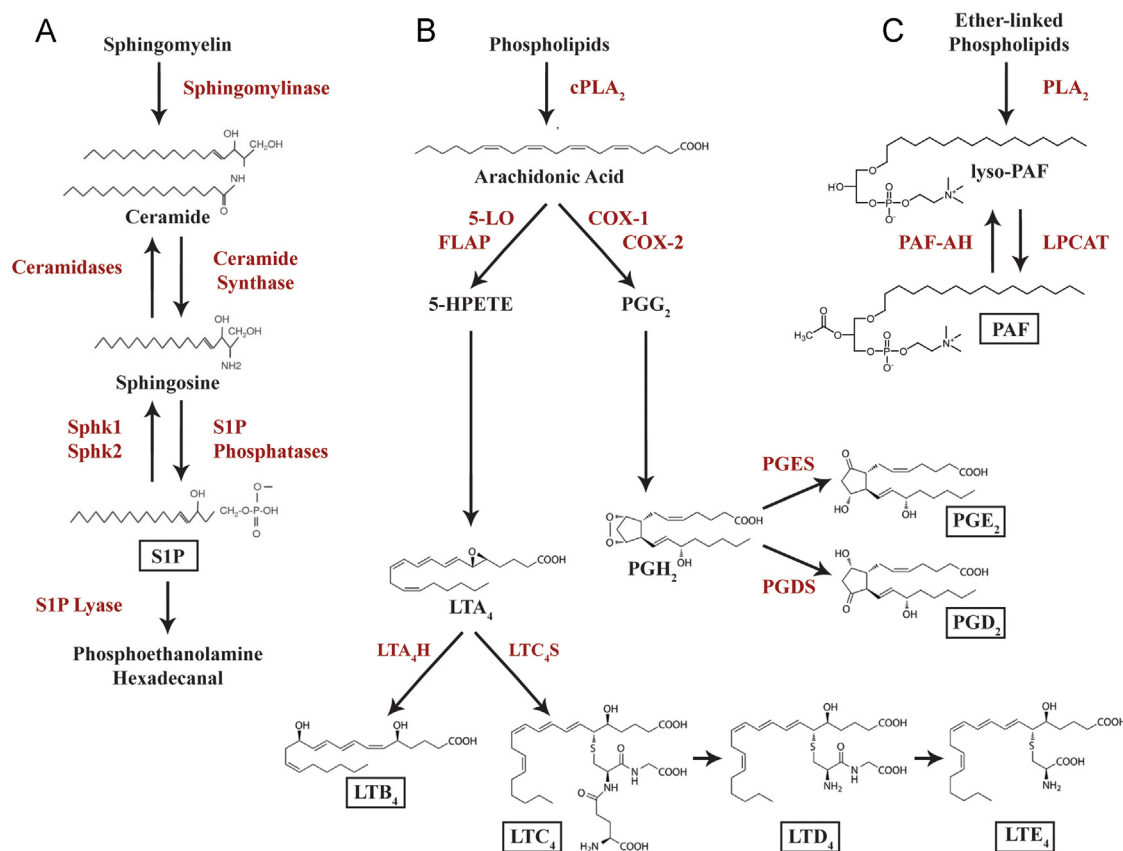


Fig. 1. Schematic representation of the biosynthesis of mast cell-associated lipid mediators. (A) Sphingosine-1-phosphate (S1P) is a metabolite of complex sphingolipids. The phosphocholine group of sphingomyelin is cleaved by sphingomyelinase to generate ceramide. The fatty acid in the ceramide moiety is then cleaved by ceramidases to produce sphingosine. Sphingosine can be phosphorylated at the primary hydroxyl group by one of two sphingosine kinases (SphK1 or 2) to form S1P. S1P is terminally degraded by S1P lyase or dephosphorylated back to sphingosine by S1P phosphatases. (B) Synthesis of eicosanoids. Cytosolic phospholipase A2 (cPLA₂) is translocated to the nuclear membrane to release arachidonic acid (AA) from the *sn*-2 position of nuclear membrane phospholipids. AA is oxidatively metabolized by cyclooxygenase (COX) and lipoxygenase (5-LO) producing the precursors for prostaglandins (PG) and leukotrienes (LT), respectively. There are two COX isoenzymes: COX-1 (constitutive) and COX-2 (inducible). Either one catalyze sequential reactions: first, two molecules of oxygen are inserted into AA, cyclizing it to produce PGG₂; next, an endoperoxidase reaction reduces PGG₂ to PGH₂. PGH₂ is a precursor for PG, prostacyclins and thromboxanes (the latter two are not depicted). PGH₂ is converted into PGD₂ by PGD synthase (PGDS) or into PGE₂ by PGE synthase (PGES). For the synthesis of LT, 5-LO is translocated to the nuclear envelope oxidizing AA to 5-hydroxyperoxyeicosatetraenoic acid (5-HPETE) and then dehydrating it to leukotriene A₄ (LTA₄). The generation of LTA₄ by 5-LO also depends on the function of 5-LO activating protein (FLAP), a perinuclear membrane protein that transfers free AA to 5-LO. Two different classes of LTs can be produced from LTA₄: LTB₄, formed by LTA₄ hydrolase (LTA₄H), and LTC₄, the parent cysteinyl leukotriene (cys-LT), formed by leukotriene C₄ synthase (LTC₄S). LTC₄ is then exported from the cell, where it is further converted to LTD₄ and LTE₄, the most stable cys-LT. (C) For the synthesis of platelet-activating factor (PAF), a fatty acid is removed from the *sn*-2 position of ether-linked phospholipids (1-alkyl-2-acyl-*sn*-glycero-3-phosphorylcholine) by phospholipase A₂ (PLA₂) to produce the intermediate lyso-PAF (1-alkyl-*sn*-glycero-3-phosphorylcholine). An acetyl group is then transferred to lyso-PAF by lyso-PAF acetyltransferase (LPCAT) to produce PAF. Deacetylation of PAF by PAF acetylhydrolase (PAF-AH) inactivates PAF.

embryogenesis and lymphocyte trafficking, respectively, processes where extracellular S1P plays important roles (Fukuhara et al., 2012; Kawahara et al., 2009). Members of the ATP binding cassette (ABC) superfamily of transporters have also been implicated in S1P transport (Maceyka and Spiegel, 2014). In activated mast cells, knockdown or pharmacological inhibition of ABCC1 significantly hinders FcεRI-dependent export of S1P (Mitra et al., 2006). It remains to be determined whether Spns2 or other ABC transporters play a contributory role in the export of S1P from mast cells.

2.2. Effect of S1P on mast cells

2.2.1. S1PR expression and regulation of mast cell function

Mast cells have been reported to express two out of the five receptors for S1P: S1P₁ and S1P₂ receptors. S1P generated following FcεRI-mediated SphK activation was shown to induce ligand-dependent transactivation of both S1P₁ and S1P₂ (Jolly et al., 2004). Accumulated data from studies examining the role of S1P receptors on mast cell function support a model where SphK activation and S1P₁ signaling are involved in the migration of mast cells toward antigen (Jolly et al., 2004; Mitra et al., 2006) (Fig. 2). Accordingly, in a

model of food allergy, SphK-deficient mast cells failed to migrate to the gastric mucosa in response to antigen challenges (Diesner et al., 2012). Pharmacological inhibition, genetic deletion or knockdown of SphK or S1P₁ receptor in mast cells inhibited chemotactic motility towards antigen or SCF without affecting chemotaxis towards S1P, suggesting an autocrine function for antigen or SCF-generated S1P (Dillahunt et al., 2013; Jolly et al., 2004; Olivera et al., 2006). In support for this concept, inhibition of ABCC1-mediated S1P export blocks migration of mast cells to antigen *in vitro*, an effect that is rescued by addition of S1P (Mitra et al., 2006).

S1P₂ receptor, on the other hand, has been described to enhance FcεRI-induced degranulation (Jolly et al., 2004; Mitra et al., 2006; Olivera et al., 2006) (Fig. 2). However, this effect may depend on the type of mast cell and is likely influenced by environmental cues that may affect S1P₂ receptor expression (Jolly et al., 2004; Olivera, 2008). Our data using S1P₂-deficient mast cells did not support a role for S1P₂ receptors in the degranulation of antigen-stimulated peritoneal or bone marrow derived mast cells (BMMC) differentiated in the presence of SCF and IL-3 in the culture media, and mice deficient in S1P₂ did not show alterations in antigen-induced immediate hypersensitivity

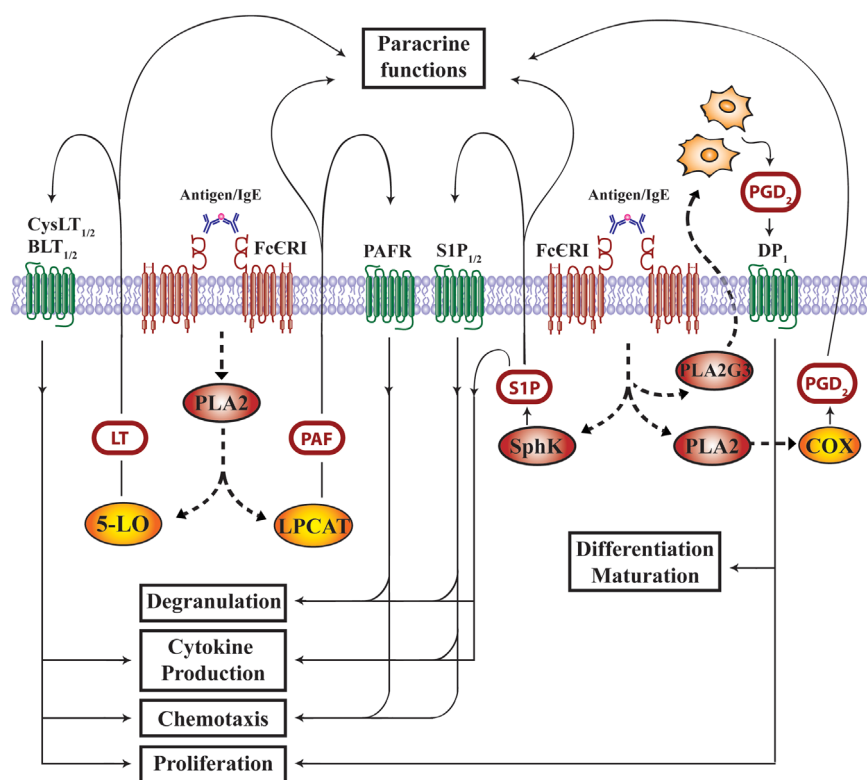


Fig. 2. Bioactive lipid mediators and their function in mast cell biology. Eicosanoids (leukotrienes (LT) and prostaglandin D₂ (PGD₂)) as well as platelet-activating factor (PAF) are generated and released by mast cells within minutes of mast cell activation, while the release of sphingosine-1-phosphate (S1P) peaks hours after activation. FcεRI induces the activation of phospholipase A₂ (PLA₂) and sequentially other enzymes depicted in Fig. 1, leading to the biosynthesis LT, PGD₂ and PAF. FcεRI aggregation also causes the early activation of sphingosine kinases (SphK) to generate S1P. These lipids are released by specific transporters (not depicted) and engage their specific GPCR in both autocrine and paracrine manners. Activation of these receptors in mast cells by mast cell generated lipid mediators can modify responses such as degranulation, cytokine production, chemotaxis and proliferation. S1P may also mediate some of these responses independently of its cell surface receptors, acting as an intracellular signaling molecule. Mast cell-expressed GPCR receptors can also be activated in a paracrine manner by lipid mediators released by other cell types, as has been described for the PGD₂ receptor DP₁. The soluble form of group III PLA₂ (PLA₂G3) secreted from mast cells increases the expression of fibroblastic, lipocalin-type PGD₂ synthase (L-PGDS). PGD₂ produced by fibroblasts, but not by mast cells, engages mast cell DP₁ receptors and promotes mast cell maturation. For clarity, the distinct receptors and functions for each particular class of lipid mediators are not depicted separately. For their detailed function, see Table 1 and the text.

reactions (Olivera et al., 2013b). However, a role for S1P₂ in FcεRI-induced degranulation was observed in BMMC differentiated only with IL-3 and in RBL-2H3 cells (Jolly et al., 2004; Olivera et al., 2013b). In human mast cells, the effect of silencing S1P₂ on degranulation varied from markedly pronounced (Mitra et al., 2006; Oskeritzian et al., 2010) to very minimal (Olivera et al., 2013b). Furthermore, when exogenous S1P alone or in combination with antigen is added to mast cells the reported effect on degranulation also varies from pronounced (Oskeritzian et al., 2010) to very marginal (Bansal et al., 2008; Jolly et al., 2004; Olivera et al., 2006). The mechanism by which S1P₂ might regulate mast cell degranulation still remains unclear. S1P does not appear to be released into the media before the occurrence of degranulation, and inhibition of ABC1-mediated S1P export does not affect FcεRI-induced degranulation (Mitra et al., 2006). Thus, an auto-crine “inside-out” model of S1P signaling is questionable, unless another type of transporter couples intracellular S1P to the cell membrane receptor. Alternatively, S1P translocated to the outer leaflet of the plasma membrane could, without being exported, enter by lateral diffusion into the binding pocket of the receptor, a potential path that was evidenced in crystallography studies of S1P₁ receptor (Hanson et al., 2012). S1P₁ has been recently shown to be present within intracellular multivesicular endosomes where it may support exosome maturation and release (Kajimoto et al., 2013). If a comparable mechanism exists for S1P₂ in mast cells, S1P generated by antigen stimulation may not require export to

mediate degranulation in certain populations of mast cells. However, these possibilities remain theoretical.

2.2.2. S1P receptor-independent effects on mast cell function

The biological effects of S1P, beyond those conferred by activation of S1P receptors, may be mediated through its binding to intracellular targets. Although not many intracellular S1P targets have been identified, it was reported that S1P interacts with TNF receptor-associated factor 2 (TRAF2) resulting in the activation of TRAF2 E3 ligase activity and modulation of NF-κB signaling (Alvarez et al., 2010). S1P can also modulate gene transcription by directly binding to histone deacetylases and inhibiting their activity (Hait et al., 2009).

Mouse mast cells lacking SphK2, which do not produce or export S1P, have a profound defect in calcium mobilization, degranulation, eicosanoid and cytokine production in response to antigen and these defects are either not restored (calcium) or partially restored (degranulation) when S1P is added exogenously (Olivera et al., 2007). This may suggest, with the exception of the considerations pointed in the section above, that S1P receptors are not major contributors to degranulation and that S1P might modulate mast cell function as an intracellular mediator (Fig. 2) or by affecting the relative levels of other lipid products such as SPH and ceramide whose effects generally oppose those of S1P (Prieschl et al., 1999). However, the demonstration that S1P effects

on early mast cell responses are linked to its direct binding to intracellular targets or that are receptor-independent (by using mast cells deficient in multiple S1P receptors) is still lacking.

2.2.3. Effect of S1P on mast cell phenotype

In addition to the role of mast cell-generated S1P on mast cell responses upon antigen stimulation, other studies suggest that S1P may act as an environmental cue that shapes the phenotype of mast cells. This was hypothesized after the observation that mast cells deficient in SphK2, which produce very little S1P and are unresponsive to allergic challenge *in vitro*, were paradoxically able to produce normal histamine responses during systemic anaphylaxis in SphK2-deficient mice. These mice exhibit elevated levels of S1P in circulation, and this might compensate for the mast cell-intrinsic inability to produce S1P during stimulation (Olivera et al., 2007). Supporting this hypothesis, the levels of S1P in different mouse strains (C57BL/6 and 129Sv) correlated with the severity of their anaphylactic responses, with the T_H1-dominated C57BL/6 mice exhibiting lower levels of S1P and anaphylactic responses (Olivera et al., 2013c) than the T_H2-dominated 129Sv strain. However, when the levels of S1P in C57BL/6 were increased by adding an inhibitor of S1P lyase in the drinking water for days before challenge, mice showed enhanced systemic anaphylactic responses similar to those in 129Sv mice, suggesting a link between S1P levels and the enhanced mast cell phenotype (Olivera et al., 2013c). In agreement, chronic exposure to S1P during differentiation of BMMC cultures resulted in a hyper-responsive phenotype that was maintained for at least two weeks after suspension of treatment and, when engrafted into mast cell-deficient Kit^{W-sh/W-sh} mice, produced stronger anaphylactic responses than untreated cells. Furthermore, defective catabolism of S1P due to S1P-lyase deficiency in BMMC resulted in a hyper-responsive phenotype and an altered gene expression landscape, supporting the idea that chronic exposure of mast cells to elevated S1P causes phenotypic changes (Olivera et al., 2013c). The specific involvement of S1P receptors in facilitating these phenotypic changes is currently unknown.

Studies in human cord blood progenitors demonstrated that chronic exposure to both S1P and SCF enhances the rate of differentiation into mast cells as well as the number of connective tissue-type mast cells (Price et al., 2009). The mechanism for how S1P induces a developmental shift in the phenotype of human mast cells appears to be partially indirect, involving the production of IL-6 by cells of the monocyte/macrophage lineage (Price et al., 2009). Altogether, these studies suggest that deregulation of S1P homeostasis in circulation or in the tissue environment by diet, genetic or environmental factors, may result in alterations in mast cell phenotype and the susceptibility to particular allergic reactions.

2.3. Effect of S1P on the allergic response

As discussed earlier, under homeostatic conditions, the levels of interstitial S1P in tissues are markedly low compared to the levels of S1P in circulation (Olivera et al., 2013a). However, changes in the tissue environment can result in local increases in S1P concentrations. For instance, in various models of acute inflammation (Keul et al., 2011; Ledgerwood et al., 2008; Roviezzo et al., 2011), S1P levels were found to be elevated in tissue exudates. Similarly, in asthma patients, S1P is elevated in the bronchoalveolar lavage hours after an allergic challenge, suggesting local changes in S1P (Ammit et al., 2001). Mast cells respond to environmental stimuli and can synthesize and release significant quantities of S1P into the media and thus have the potential to alter interstitial S1P concentrations. Because mast cells rapidly degranulate and release vasoactive mediators, S1P levels in the interstitium may immediately increase due to plasma leakage and flooding of blood-born S1P.

Active release of S1P from mast cells, which occurs at later times following stimulation, may further increase S1P levels and significantly modulate inflammatory processes. Given that S1P is an important regulator of angiogenesis, vascular permeability (Blaho and Hla, 2014) and immune cell recruitment/function (Rivera et al., 2008), the presence of mast cell-derived S1P likely contributes significantly to the regulation of allergic inflammation. Little is known, however, about the specific contributions of increased S1P on the allergic response, and both pro- and anti-inflammatory roles have been proposed. This is due, in part, to the complex nature of S1P, including the ubiquitousness of its synthesis and receptor expression, the pleiotropic biological functions of S1P, and the possible conversion of S1P to sphingosine or ceramide, which mediate distinct biological functions. The specific function of S1P during inflammation may depend on the nature of a particular antigenic challenge, the type of immune cells that respond to this challenge, and the site of action for S1P and whether the tissue has changed due to chronic inflammatory insults.

2.3.1. Pro-inflammatory roles of S1P

During the early stages of inflammation, S1P may promote inflammation by attracting diverse immune cells to the site (Arnon and Cyster, 2014; Rivera et al., 2008; Spiegel and Milstien, 2011) or by retaining hematopoietic stem cell progenitors (Massberg et al., 2007) and mature T cells in tissues through increased adhesion to the afferent lymphatic endothelium (Ledgerwood et al., 2008). Several reports suggest that S1P can also affect the nature of immune responses by polarizing CD4⁺ T cells into different subsets. While some studies find that S1P skews T cell responses toward allergic T_H2-phenotypes and disfavors T_H1-cell responses, either directly or partly mediated by its effects on DCs (reviewed in Rivera et al., 2008), others indicate that S1P, via the S1P₁ receptor, suppresses the differentiation of both thymic and extrathymic T-reg cells and promotes T_H1-cell differentiation (Liu et al., 2010). In addition, S1P has also been reported to promote T_H17 differentiation via T cell-expressed S1P₁ receptor (Garris et al., 2013; Huang et al., 2007) or indirectly, via DC-expressed S1P₄ receptor (Schulze et al., 2011). The exact conditions that define these different outcomes are not entirely clear. In aggregate, the notion remains that S1P may serve as a pro-inflammatory signal by promoting T cell effector differentiation and by suppressing T-regs, a T cell subset that also modulates antigen-induced responses in mast cells (Gri et al., 2008). This may be particularly relevant in cases of recurrent allergic reactions such as those seen with allergic asthma (Galli and Tsai, 2012), where repeated increases in S1P (and other mediators) produced by mast cells can thus contribute to chronic inflammation. In addition, the repeated challenges inherent to chronic allergic diseases cause tissue remodeling characterized by epithelial cell injury and structural changes in vascular, smooth muscle and connective tissues, many of which have been shown to be affected by S1P (reviewed in Ryan and Spiegel, 2008).

2.3.2. Anti-inflammatory roles of S1P

Other lines of evidence suggest, however, an anti-inflammatory role for S1P. Skin biopsies of individuals with atopic dermatitis (Seo et al., 2006) and psoriasis (Mechtcheriakova et al., 2007) show increased expression of two enzymes involved in the degradation of S1P, S1P lyase and S1P-phosphatase type 2 (SPP2), respectively (Fig. 1). In agreement, the degradation of S1P was increased and S1P levels reduced in lesional skin of dogs with atopic dermatitis compared to normal skin (Baumer et al., 2011). A possible interpretation is that low S1P levels allow for perpetuation of the disease, which infers a protective role for S1P. Topical application of S1P to the ear in mouse models of dermatitis or psoriasis reduced ear swelling and hyperproliferation of the skin

(Reines et al., 2009; Schaper et al., 2013). Furthermore, inhalation of S1P or the S1P mimetic FTY720 suppressed airway inflammation and bronchial hyperresponsiveness in a model of allergic asthma (Idzko et al., 2006). In both models, the mechanism for such suppression involved prevention of dendritic or Langerhans cell migration to the lymph nodes (Idzko et al., 2006; Reines et al., 2009) and in the dermatitis model, reduced antigen processing via S1P₂ receptor activation (Japtok et al., 2012). S1P has also been reported to exert anti-inflammatory roles by promoting the switch from the pro-inflammatory M1 to the anti-inflammatory M2 macrophage subtype (reviewed in Rivera et al., 2008).

2.3.3. A protective role for non-mast cell derived S1P in anaphylaxis

S1P production during systemic anaphylaxis, a severe and sometimes fatal allergic reaction affecting multiple organs, may help reduce the severity of anaphylactic shock (Olivera et al., 2010). Even though the cellular source for protective S1P during systemic anaphylaxis is not the mast cell and is non-hematopoietic (Olivera et al., 2010), it will be briefly discussed here because of the important implications for anaphylaxis.

In models of passive IgE/antigen- or histamine-induced anaphylaxis (Olivera et al., 2013b; Olivera et al., 2010) S1P is produced via SphK1 (probably in the vascular beds) and facilitates recovery from anaphylaxis via the activation of S1P₂, which counteracts vasodilation and hypotension. In more severe models of anaphylaxis, such as those induced by PAF (Camerer et al., 2009; Cui et al., 2013), IgE clone SPE-7 (Camerer et al., 2009; Olivera et al., 2013b) and active systemic anaphylaxis (Cui et al., 2013), S1P₁ (Camerer et al., 2009) and S1P₂ (Cui et al., 2013) were shown to be protective by regulating inter-endothelial cell gaps and vascular permeability. S1P₂ suppressed endothelial nitric oxide synthase (eNOS) stimulation and NO production associated with anaphylaxis, thus controlling the disassembly of adherens junctions in the endothelium and excessive permeability (Cui et al., 2013). Thus, while it appears that the generation of S1P during anaphylaxis and/or the presence of S1P in circulation may be of importance for the recovery from shock, the dominant involvement of S1P₁ and S1P₂ in maintaining vascular tone or vascular barrier integrity may depend on the strength or type of stimuli, being their role on vascular integrity revealed under circumstances where vascular leakage is most severe. Although the function of S1P receptors in human anaphylaxis has not yet been explored, based on the mouse models and the beneficial effect of S1P injection in histamine-induced anaphylaxis (Olivera et al., 2010), it is tempting to speculate that a combination of S1P₁ and S1P₂ agonists could be an option for alternative anaphylaxis treatments. Other studies, however, have pointed to a role for S1P₂ in promoting endothelial cell permeability and inflammatory responses of the endothelium during endotoxemia (Sanchez et al., 2007; Zhang et al., 2013) and thus, it still remains to be understood how the same receptor can counteract PAF-induced vasopermeability while promoting permeability by other inflammatory insults.

3. Eicosanoids

Eicosanoids are biologically active lipids derived from the oxidation of 20-carbon fatty acids, particularly the polyunsaturated and essential fatty acid arachidonic acid (AA), and include prostaglandins, thromboxanes, leukotrienes and other oxygenated derivatives. By the early 1980s, it was recognized that activated mast cells could rapidly release abundant quantities of AA and subsequently metabolize it to prostaglandin D₂ (PGD₂) and cysteinyl leukotrienes (Cys-LT) (also known as slow reacting substance of anaphylaxis) with potent inflammatory effects in allergic diseases (Lewis and Austen, 1981). Consequent studies revealed that although mast cells can generate

leukotriene B₄ (LTB₄), the cysteinyl leukotriene C₄ (LTC₄) and PGD₂ upon activation, the specific profile or relative amounts of eicosanoid generation varies in both human and rodent mast cells depending on the tissue of origin, the stage of differentiation and culture conditions (Lundstrom et al., 2013; and reviewed in Boyce, 2007). PGE₂ has not been considered to be an eicosanoid abundantly produced by antigen-stimulated mast cells in culture (Boyce, 2007) although a recent report detected higher intracellular content of PGE₂ than other prostanoids by mass spectrometry in mast cells isolated from inflamed tissue in a delayed type hypersensitive model (Thomas et al., 2014). Even though the release of eicosanoids by antigen-activated mast cells requires several enzymatic steps for their *de novo* production (Fig. 1) and transporter-mediated export (Fletcher et al., 2010), it occurs rapidly (within 10–30 min), contributing to early onset allergic responses.

3.1. Prostaglandins

3.1.1. Prostaglandin D₂

PGD₂ production is mediated by the sequential enzymatic activities of cyclooxygenase (COX) and prostaglandin D₂ synthase (PGDS) (Murakami et al., 1994) (Fig. 1). Although other cells also produce PGD₂, mast cells may be a predominant source of PGD₂ (and its metabolites) in peripheral tissues affected by allergic pathologies such as nasal polyposis (Nantel et al., 2004), eosinophilic chronic rhinosinusitis with nasal polyps (Cao et al., 2014) and eosinophilic esophagitis (Abonia et al., 2010). Indeed, PGD₂ has been proposed as a selective indicator of mast cell activation in some diseases such as bronchial asthma and mastocytosis (Bochenek et al., 2004; Morrow et al., 1995). The transcription of enzymes involved in PGD₂ synthesis in mast cells is enhanced by inflammatory and environmental signals, and this can augment the PGD₂ response to antigen stimulation (Diaz et al., 2006; Murakami et al., 1994; Murakami et al., 1995). Mast cells (as well as macrophages, dendritic cells and T_H2 cells) express the hematopoietic isoform of PGDS (H-PGDS) and two isoforms of COX, constitutive (COX-1) and inducible (COX-2). COX-1 is involved in the immediate production of eicosanoids, while COX-2 has been implicated in a delayed phase of PGD₂ synthesis (Diaz et al., 2006; Murakami et al., 1994), which appears to be associated with the resolution of inflammation (Scher and Pillinger, 2009).

3.1.1.1. Effect of PGD₂ on mast cells. PGD₂ actions are mostly mediated by two GPCRs receptors, DP₁ and DP₂ (also known as chemoattractant receptor-homologous molecule expressed on T_H2 cells (CRTH2)) (Boyce, 2007) (Table 1). While DP₂ is expressed in mast cells, its location in human mast cells was reported to be mostly intracellular and thus they were unresponsive to DP₂ agonists alone or in combination with IgE/Ag (Moon et al., 2014). In a mouse model of IgE/Ag-dependent passive cutaneous anaphylaxis, deficiency in DP₂ caused increased edema (Taketomi et al., 2013). This may suggest a protective effect of DP₂ receptors against vascular leakage or an inhibitory role of this receptor on mast cell degranulation *in vivo*, which contrasts with the finding that DP₂ receptor activation enhances FcεRI-mediated histamine release in basophils (Yoshimura-Uchiyama et al., 2004). Thus, the function of DP₂ receptors in mast cells and the mechanism regulating its intracellular location are still unclear.

A recent elegant study uncovered a role for DP₁ receptors on the maturation of mast cells, rendering them more responsive to IgE-mediated biological responses (Taketomi et al., 2013) (Table 1 and Fig. 2). The pathway leading to the activation of DP₁ involved a cross-talk between mast cells and fibroblasts whereby a soluble form of group III PLA2 (PLA2G3) secreted from activated mast cells increases the expression of fibroblastic, lipocalin-type PGD₂

Table 1

Lipid mediator receptors most abundantly expressed on mast cells, their functions on mast cells and on the allergic response.

Mast cell-expressed GPCR	Lipid agonist	Gα coupled to	Effect on mast cell biology	Effects on allergic responses
S1P ₁	S1P	Gi	Chemotaxis (+)	Vascular permeability (–) Angiogenesis (+), endothelial cell junctions (+) Immune cell trafficking (+)
S1P ₂	S1P	Gq, G _{12/13}	Degranulation (+)	Vascular permeability (+/–) Vasoconstriction, blood pressure regulation Chemotaxis of immune cells (+/–)
DP ₁	PGD ₂	Gs	Promotes maturation and responsiveness to IgE/Ag	Suppresses T _H 1-driving cytokines
DP ₂ (CRTH2)	PGD ₂	Gi	Variable effects on degranulation	Epithelial activation Inhibition of dendritic cell migration
CysLT _{1/2}	Cys-LTs	Gi, Gq-CysLT ₁	Degranulation (+) Cytokine production (+) Proliferation (+)	Inflammatory cell recruitment, activation of T _H 2 cells Inflammatory cell recruitment Vascular permeability (+) Bronchoconstriction Immune cell function
BLT _{1/2}	LTB ₄	Gi	Chemotaxis (+) Production of Th2-promoting cytokines	Inflammatory cell recruitment
PAFR	PAF	Gi, Gq ₁₁	Chemotaxis (+) Degranulation (+)	Bronchoconstriction, airway hyperreactivity Vascular permeability (+), hypotension, cardiovascular dysfunction

This table includes only lipid mediator receptors expressed on mast cells that bind lipids abundantly released by mast cells. Non-classical leukotriene receptors are not included.

synthase (L-PGDS). Fibroblast L-PGDS produces PGD₂ and, in a paracrine manner, engages mast cell DP₁ receptors, which induce the expression of mast cell proteases, histidine decarboxylase (that produces histamine) and cell surface FcεRI. Mice deficient in PLA2G3, L-PGDS (expressed by fibroblasts) or DP₁, and mast cell-deficient mice reconstituted with PLA2G3-null or DP₁-null mast cells develop abnormal mast cell phenotypes and reduced responses to systemic or passive cutaneous anaphylaxis, demonstrating that bioactive lipids such as PGD₂ may be important cues in the local environment regulating mast cell maturation and responsiveness. Interestingly, deficiency in mast cell-intrinsic H-PGDS seemed to have slightly enhanced cutaneous anaphylaxis reactions in contrast to the attenuated responses in mice lacking fibroblast-intrinsic L-PGDS, which raises the interesting question of how mast cells discriminate between the different pools of PGD₂ (Taketomi et al., 2013), a mechanism that needs further investigation.

3.1.1.2. Effect of PGD₂ on the allergic response. PGD₂ produced mostly by mast cells during the early phase of an allergic reaction has been considered an essential link between the early and late-phase of inflammation by promoting the recruitment of inflammatory cells (Naclerio et al., 1985). DP₁ receptors are expressed in dendritic cells and T_H1 cells, but not in significantly in T_H2 cells while DP₂ receptor is viewed as a specific marker for human T_H2 cells (Pettipher, 2008; Xue et al., 2005). Both DP₁ and DP₂ receptors may support a T_H2-type inflammatory profile. Whereas DP₂ is the major PGD₂ receptor contributing to the recruitment of T_H2 cells, eosinophils and basophils and promoting T_H2 cytokine production (Hirai et al., 2001; Xue et al., 2005), DP₁ supports T_H2 polarization by suppressing the production of T_H1-driving cytokines such IL-12 in dendritic cells (Faveeuw et al., 2003; Pettipher, 2008).

In addition to immune cell recruitment, infusion of PGD₂ in humans causes nasal stuffiness, hypotension, and flushing, suggesting an overall participation for PGD₂ in immediate hypersensitivity processes (Boyce, 2007; Pettipher, 2008). The higher expression of PGDS, DP₁ and DP₂ receptors in the nasal mucosa of patients with allergic rhinitis is also consistent with a role for PGD₂ in nasal congestion and inflammatory cell infiltration (Nantel et al., 2004). Indeed, a reduction in rhinitis symptoms has been observed after treatment of perennial rhinitis with ramatroban, an

effect that has been attributed to its antagonistic effects on DP₂ receptors (Pettipher and Whittaker, 2012). Asthma severity also was found to associate with PDG₂ in BAL fluid as well as increased H-PGDS (mostly from mast cells) and DP₂ expression levels (Fajt et al., 2013). The use of DP₂ antagonists has shown relatively modest but significant results in recent clinical trials in some asthmatic populations (reviewed in Fanning and Boyce, 2013). A potential role for PGD₂ in aspirin exacerbated respiratory disease (AERD) was revealed in a subset of patients unable to tolerate desensitization to aspirin. These patients showed an overproduction of PGD₂ associated with cutaneous and gastrointestinal symptoms after oral aspirin challenge, while patients successfully desensitized exhibited a sharp decrease in PGD₂ production (Cahill et al., 2014).

It is important to note, however, that in chronic allergic diseases or delayed hypersensitivity, the role of PGD₂ and its receptors may be more complex, involving not only pro-inflammatory functions but also roles in the resolution of inflammation (Boyce, 2007; Rajakariar et al., 2007; Scher and Pillinger, 2009). In part, the pro-resolution effects of PGD₂ may be mediated by its dehydration into prostaglandin J₂ (15d-PGJ₂), a molecule that binds the intracellular peroxisome proliferator-activated receptor-γ (PPAR-γ), although not all the anti-inflammatory effects of PGJ₂ appears to be dependent on PPAR-γ (Scher and Pillinger, 2009; Trivedi et al., 2006).

3.1.2. Prostaglandin E₂

Prostaglandin E₂ (PGE₂) is synthesized in multiple cell types following COX and prostaglandin H synthase (PGHS) activation (Fig. 1). When released to the extracellular media, PGE₂ can activate and signal through four specific GPCRs in target cells (EP₁₋₄) that vary in sensitivity, signaling mechanisms and susceptibility to desensitization, and thus it is not surprising that PGE₂ exerts varied cellular responses and mediates pro- and anti-inflammatory functions (reviewed in Boyce, 2007; Kalinski, 2012; Scher and Pillinger, 2009; Torres et al., 2014). Mast cells do not appear to be a relevant source for this eicosanoid and thus, the roles of PGE₂ in allergy will not be discussed here, but we will briefly highlight the concept that PGE₂, through its actions on mast cells, may modulate allergic inflammation.

For instance, PGE₂ inhalation before allergen challenge in asthmatic individuals has been known to prevent allergen-induced airway hyperreactivity and inflammation (Gauvreau et al., 1999; Hartert et al., 2000). In mouse asthma models, the anti-inflammatory function of PGE₂ has been associated with the inhibition of lung mast cell activity (reviewed in Torres et al., 2014). PGE₂ dampens FcεRI-induced mediator release in human lung mast cells and certain mast cell subtypes via the Gα_s-coupled EP₂ receptors, while it enhances responses in other mast cell types mostly when acting through the Gα_i-coupled EP₃ receptor (Boyce, 2007; Kay et al., 2013; Serra-Pages et al., 2012; Torres et al., 2014). Indeed, variations in the ratio of EP₂/EP₃ expression in various subtypes of mast cells appears to be a main determinant of the effect of PGE₂ on mast cell function (Serra-Pages et al., 2012). Although the involvement of mast cells in the mitigation of asthma by PGE₂ has not been fully demonstrated, the use of specific EP₂ agonists, which may evade additional and sometimes unwanted effects of PGE₂, is an interesting avenue that needs further exploration in the treatment of mast cell-driven allergic diseases and asthma.

3.2. Leukotrienes

While prostaglandins can be synthesized by most cell types, leukotrienes (LTs) are generated by inflammatory cells such as mast cells, macrophages, and neutrophils. In mast cells, activation of FcεRI receptors induces the activation of the enzyme 5-lipoxygenase (5-LO) to produce leukotriene A₄ (LTA₄), the precursor of LTB₄ as well as LTC₄, the parent cyteinyl leukotriene (Cys-LT) (Fig. 1). The biological activity of Cys-LTs is largely mediated through two GPCRs referred to as CysLT₁ and CysLT₂, while LTB₄ signals through BLT₁ and BLT₂ receptors (Table 1). Other leukotriene receptors, however, have also been described (Kanaoka and Boyce, 2014; Tager and Luster, 2003). Leukotrienes have long been implicated in allergies and their important and complex contributions to different processes during the allergic response have been recently summarized in excellent reviews (Boyce, 2007; Kanaoka and Boyce, 2014; Laidlaw and Boyce, 2012). Thus, here we will focus on some aspects of the autocrine functions of leukotrienes on mast cells.

3.2.1. Effect of leukotrienes on mast cells

Human mast cells express both CysLT₁ and CysLT₂ receptors and respond to Cys-LTs by mobilizing calcium, releasing pro-inflammatory cytokines and chemokines, and mediating proliferation (Mellor et al., 2001; Paruchuri et al., 2008) (Fig. 2). Interestingly, the responses to Cys-LTs (as well as those to IgE/antigen) on human mast cells are greatly enhanced by priming with T_H2 cytokines, particularly IL-4 (Hsieh et al., 2001; Mellor et al., 2002), an effect mediated in part by an increase in the transcription of LTC₄ synthase (LTC₄S) (Hsieh et al., 2001) and in the cell surface expression of CysLT₂ receptor (Mellor et al., 2003). The CysLT₁ receptor is mostly responsible for the augmented mast cell responses to Cys-LTs or to IgE/antigen after IL-4 priming, although CysLT₂ and other putative Cys-LT receptors have been reported to contribute (Mellor et al., 2002; Mellor et al., 2003; Paruchuri et al., 2008). IL-4 is produced during allergic inflammation and regulates mast cell proliferation, T_H2 cytokine production and FcεRI receptor expression (Lorentz et al., 2005). Thus, the finding that IL-4 regulates Cys-LT synthesis and function may suggest roles for these lipids in the amplification of IL-4 and antigen-induced responses. This may be particularly relevant during the allergic response.

Indeed, IL-4 induces mast cell proliferation partly through the production of Cys-LT, engagement of CysLT₁ receptors and transactivation of the receptor for SCF (Jiang et al., 2006), KIT, which is critical for mast cell differentiation, proliferation and function. Thus, the mitogenic pathways induced by CysLT₁ receptors are in part convergent with those of KIT, but also distinct (Jiang et al., 2006), as

supported by the synergistic effects of Cys-LT and SCF on the proliferation of mast cells (Al-Azzam et al., 2014). On the other hand, SCF can also induce Cys-LT production in mast cells and blockage of its production or antagonism of CysLT₁ receptor *in vivo*, substantially reduces the airway hyperresponsiveness induced after intra-tracheal instillation of SCF in mice (Oliveira et al., 2001). Thus, Cys-LTs can be at the crossroads of FcεRI, IL-4 receptor and KIT pathways, and the regulation, crosstalk and synergy between these pathways may contribute to mast cell hyperplasia and hyper-reactivity during allergic inflammation, a condition where all these regulators are known to be important. This notion is supported by the findings of attenuated airway inflammation and T_H2 cytokine production as well as reduced hyperplasia and activation of tracheal intraepithelial mast cells in LTC₄S-deficient mice subjected to antigen-induced pulmonary inflammation (Kim et al., 2006).

Mast cells express also the LTB₄ receptors, BLT₁ and BLT₂ (Table 1). Both receptors were shown to induce chemotaxis in response to LTB₄ (Lundeen et al., 2006), although this effect is particularly prominent in immature mast cells, where the expression of BLT₁ is increased compared to mature mast cells (Weller et al., 2005). Indeed, intradermal injection of LTB₄ *in vivo* induced the recruitment of mast cell progenitors to sites of inflammation (Weller et al., 2005). In addition, the BLT₂ receptor may mediate, in an autocrine manner, the production of T_H2 cytokines by mast cells after FcεRI activation (Cho et al., 2010) (Fig. 2). LTB₄ released by mast cells during an allergic trigger may contribute to the recruitment of inflammatory cells as well as circulating mast cell progenitors, perpetuating inflammation.

4. Platelet-activating factor (PAF)

Platelet-activating factor (PAF) is a lipid mediator with an important role in allergy, asthma, as well as other pathological processes, acting through its receptor (PAFR) (Prescott et al., 2000; Tsoupras et al., 2009) (Table 1). PAF was originally described as a substance released by basophils in an IgE-dependent process, capable of inducing platelet aggregation. PAF generation by mast cells, basophils and other blood cells requires the activity of PLA₂ and a lyso-PAF acetyltransferase (Prescott et al., 2000) (Fig. 1). PAF is released during the early phase of the allergic response but has a very short half-life (3–13 min) due to its inactivation by PAF acetylhydrolase.

4.1. Effects of PAF on mast cells

PAF induces mast cell chemotaxis (Nilsson et al., 2000) and mediator release (Fig. 2). The effects of PAF on mast cell release may vary depending on the mast cell type and the levels of PAF receptor expression. Whereas PAF induced histamine and PGD₂ release in mast cells from human lung or derived from adult peripheral blood progenitors, it was ineffective in human skin mast cells *in vitro*, which do not express the receptor (Kajiwara et al., 2010). However, it can induce degranulation *in vivo* from skin mast cells when injected intradermally, an effect that may be secondary to its activation of neural reflexes (Petersen et al., 1997). It has been suggested that PAF, released by mast cells or other cells during anaphylaxis may contribute to the dissemination of a mast cell response to an allergen at sites distal to allergen exposure (Kajiwara et al., 2010).

4.2. Effects of PAF on the allergic response

The effects of PAF as a bronchoconstrictor and mediator of airway hyperreactivity in bronchial asthma have long been recognized, although the use of PAF inhibitors as a therapeutic option in asthma has been ineffective (Kasperska-Zajac et al., 2008). PAF also causes severe hypotension and cardiovascular dysfunction during

acute anaphylaxis, an effect that, at least in mice, is dependent on a PAF-mediated activation of eNOS and consequent NO formation (Cauwels et al., 2006). In mouse models, PAF antagonists effectively attenuated IgG-induced anaphylaxis (Jiao et al., 2014; Jonsson et al., 2011; Strait et al., 2002; Tsujimura et al., 2008) and peanut-induced anaphylaxis severity (Arias et al., 2009), but did not effectively attenuate IgE-mediated anaphylaxis, which is more dependent on histamine release (Strait et al., 2002). In humans, it has not been clearly established whether anaphylaxis is mediated through a classical IgE-mediated pathway, an alternative IgG-mediated pathway or both (Finkelman, 2007). However, some studies have reported that the levels of PAF in serum correlates with the severity of the anaphylactic reaction while histamine or tryptase levels do not, and PAF acetylhydrolase activity, the enzyme responsible of PAF inactivation, inversely correlates with severity scores (Vadas et al., 2008), and thus PAF antagonists, alone or in combination with other drugs, may be a consideration as rescue therapy for acute anaphylaxis reactions.

5. Concluding remarks

Accumulating evidence for the last twenty years have demonstrated that lipid mediators generated by mast cells are critical for the pathogenesis of allergic diseases, yet a full understanding of their intricate and finely tuned participation is incomplete. While mast cell-derived lipid mediators and their receptors represent attractive therapeutic targets for treating allergic inflammation, the pleiotropic functions and complex biology associated with these molecules and the realization of the existence of previously unrecognized receptors mediating some of their actions, pose a significant challenge to researchers who seek to understand and modulate the disease processes they regulate.

To date, several compounds that target lipid mediators have been employed in a clinical setting and the interest in developing and investigating new and more specific compounds is expanding. The S1P receptor modulator, FTY720, was the first FDA-approved sphingo-mimetic oral therapeutic and has been used to treat relapsing-remitting multiple sclerosis (Bigaud et al., 2014), but its local application to treat allergic diseases has been thus far restricted to animal models. Development of more selective agonist and antagonists for S1P receptors or anti-S1P antibodies to locally intercept its actions (Bigaud et al., 2014) may provide interesting therapy options in allergic inflammation and anaphylaxis. While the DP₂ receptor antagonist OC000459 has shown promising effects for asthma patients in phase 2 clinical trials, the dual DP₁/DP₂ antagonist AMG 853 has proven to be less efficacious (reviewed in Fanning and Boyce, 2013). There are also several specific Cys-LT receptor antagonists (zafirlukast, pranlukast, and montelukast) as well as LT synthesis inhibitors (zileuton) that are in clinical use with variable efficacy (Laidlaw and Boyce, 2012; Montuschi and Peters-Golden, 2010). More recently, a 5-lipoxygenase-activating protein (FLAP) (Fig. 1) inhibitor (GSK2190915) has been shown to be effective in inhibiting allergic responses to inhaled allergen in patients with mild asthma (Kent et al., 2013). The continued development and refinement of compounds that modulate receptors and signaling associated with mast cell-derived lipid mediators will continue to aid in the treatment of human disease and our understanding of the biology these molecules influence.

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