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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; BLT_{1-2}, leukotriene B4 receptors 1 to 2; BMMC, bone marrow derived mast cells; COX, cyclooxygenase; Cys-LT, cysteinyl leukotrienes; $CysLT_{1-2}$, cysteinyl leukotriene receptors 1–2; DP_{1-2}, 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; LTB_4, leukotriene B4; LTC_4, leukotriene C4; LTC_4S, leukotriene C4 synthase; eNOS, endothelial nitric oxide synthase; NO, nitric oxide; PLA_2, phospholipase A2; PAF, platelet activating factor; PGD_2, prostaglandin D2; PGE_2, prostaglandin E2; PGDS, prostaglandin D synthase; PI3K, phosphatidylinositol-4,5-bisphosphate 3-kinase; SphK, sphingosine kinase; S1P, sphingosine-1-phosphate; $S1P_{1-5}$, 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 Gα 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., 2015; 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 ($S1PR_{1-5}$) (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 (Dillahunt 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) (Dillahunt et al., 2013; Olivera et al., 2006; Oskeritzian 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 (Dillahunt 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