



# Modulation of Mast Cell Reactivity by Lipids: The Neglected Side of Allergic Diseases

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Mast cells (MCs) have long been mainly regarded as effector cells in IgE-associated allergic disorders with potential immunoregulatory roles. Located close to the allergen entry sites in the skin and mucosa, MCs can capture foreign substances such as allergens, toxins, or noxious substances and are exposed to the danger signals produced by epithelial cells. MC reactivity shaped by tissue-specific factors is crucial for allergic responses ranging from local skin reactions to anaphylactic shock. Development of Th2 response leading to allergen-specific IgE production is a prerequisite for MC sensitization and induction of FcεRI-mediated MC degranulation. Up to now, IgE production has been mainly associated with proteins, whereas lipids present in plant pollen grains, mite fecal particles, insect venoms, or food have been largely overlooked regarding their immunostimulatory and immunomodulatory properties. Recent studies, however, have now demonstrated that lipids affect the sensitization process by modulating innate immune responses of epithelial cells, dendritic cells, and NK-T cells and thus crucially contribute to the outcome of sensitization. Whether and how lipids affect also MC effector functions in allergic reactions has not yet been fully clarified. Here, we discuss how lipids can affect MC responses in the context of allergic inflammation. Direct effects of immunomodulatory lipids on MC degranulation, changes in local lipid composition induced by allergens themselves and changes in lipid transport affecting MC reactivity are possible mechanisms by which the function of MC might be modulated.

**Keywords:** mast cells, degranulation, allergy, lipids, lipid mediators, flippases, floppases, scramblases

## INTRODUCTION

Mast cells are long-living tissue-resident hematopoietic cells equipped with secretory granules containing a broad spectrum of biologically active mediators such as histamine, proteases, and cytokines (1, 2). Preferentially located in the skin and mucosa, MCs detect potentially dangerous or noxious substances in concert with danger signals produced by epithelial cells at damaged barriers. Extensive MC degranulation as an urgent response to different types of stimulation and its wide-ranging local or systemic effects are the reasons why MCs are the main effector cells in allergies (3). Here, we summarize recent findings describing how reactivity of MCs can be modulated by lipids and discuss how interference with intracellular lipid transport could affect MC reactivity.

## LIPID STRUCTURE AND MOLECULAR FEATURES

Lipids are overall hydrophobic or amphipathic molecules consisting of a hydrophilic head group and a hydrophobic tail group connected either by esters or ether bonds. Other lipids like sterols consist of a ring structure with various modifications. Lipids, in contrast to proteins and nucleic acids, are synthesized by a series of specific interlinked enzymatic reactions generating a high diversity of different lipid molecules. According to their hydrophobic characteristics and chemically functional backbones, lipids are categorized into eight main groups, namely fatty acyls, glycerolipids, glycerophospholipids, sphingolipids, sterol lipids, prenol lipids, saccharolipids, and polyketides (<http://www.lipidmaps.org>). Lipids are essential in storage of energy, arrangement of signaling complexes, participation in signal processing as second messengers and building of membranes as physical barriers. Membranes in mammalian cells consist mainly of sphingolipids, glycerophospholipids, and cholesterol (4). They are fluidic bilayers characterized by different lipid compositions in their inner and outer sides where lipids together with proteins form highly ordered structures essential for organization of cellular compartments. An integral part of membranes is cholesterol. It is synthesized in the endoplasmic reticulum (ER), transported then to the Golgi complex, and further to the plasma membrane which shows the highest cholesterol concentration. Together with sphingolipids, cholesterol regulates the membrane permeability and facilitates organization of ordered protein islets. Glycerophospholipids and sphingolipids are also synthesized in the ER and further modified in the Golgi complex as well as the mitochondria (5–7). The lysosome, on the other hand, plays a crucial role in lipid sorting and metabolism (8). Enzymatically induced changes in the lipid composition of the membrane are associated with a new ordering of membrane proteins and altered membrane microdomains (9). In general, any change in the lipid or protein compartment of a membrane affects both partners and is therefore tightly controlled by the cell. MCs in particular undergo dramatic membrane reorganization while degranulation and recovery. The schematic structure of the different lipid categories and exemplary representatives of these categories with effects on MC functions are summarized in **Table 1**.

## PRODUCTION OF LIPID MEDIATORS IS ASSOCIATED WITH CHANGES IN MAST CELL REACTIVITY

Activated in settings of allergic responses, mainly through stimulation of the high affinity receptor FcεRI complex by IgE-recognizing specific antigens, MCs release pre-stored biogenic amines, proteases, proteoglycans, chemokines as well as cytokines. In addition, MCs are well-known producers of different lipid mediators such as leukotrienes (LT) and prostaglandins (PG) (14, 20, 35) and production of these lipid mediators has in turn been shown to regulate MC functions. For example, MC-produced lipid mediators have been found to enhance inflammation in specific situations (36, 37) or

to limit inflammation in other circumstances associated with reestablishment of tissue homeostasis (38, 39). Recent studies also demonstrated that enzymes responsible for production of lipid mediators belong to the MC-specific gene expression signature (40). Furthermore, *in vitro* generated connective tissue-like MCs and mucosal-like MCs differ in their eicosanoid patterns (41) and skin MCs are unique in showing the lowest expression levels of *Alox5* gene encoding 5-lipoxygenase (40), indicating that lipid mediator production is coordinated by tissue-specific regulatory mechanisms. Production of eicosanoid mediators, sphingolipid metabolites, and platelet-activating factor (PAF) by MCs is extensively reviewed elsewhere (15, 42). Thus, during allergic responses, MCs produce a variety of lipid mediators acting in a paracrine and autocrine manner. In addition, MC reactivity is modulated by lipid mediators produced by other cells exposed to environmental challenges.

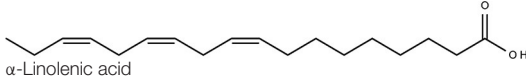
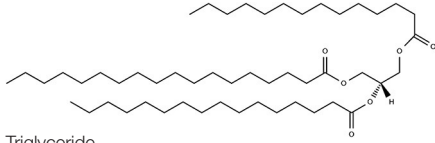
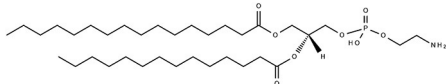
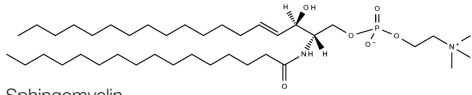
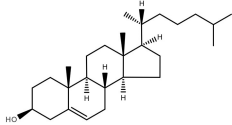
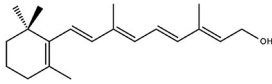
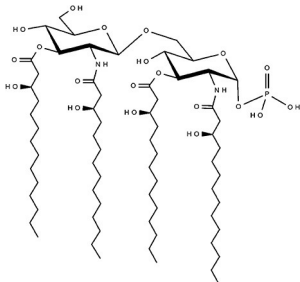
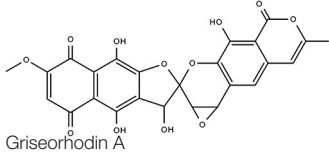
## ENDOCANNABINOIDS AFFECT MAST CELL REACTIVITY

Often overlooked regarding their modulatory effects on MC function are endocannabinoids—a group of bioactive lipids serving as secondary immune modulators participating in down-regulation of inflammatory processes (17, 43). The best characterized members of endocannabinoid lipid mediators are N-arachidonylethanolamine (anandamide, AEA) and 2-arachidonoylglycerol (2-AG) (44, 45), which are derived from membrane phospholipids in response to physiological or pathological stimuli. Furthermore, new signaling mechanisms for intracellular transport and storage of endocannabinoids have been described (46–49). Endocannabinoids act through type-1 (CB1) and type-2 (CB2) G protein-coupled cannabinoid receptors, G protein-coupled receptor GPR55, transient receptor potential channel of the vanilloid subfamily 1 (TRPV1), and peroxisome proliferator-activated receptor  $\gamma$  (PPAR  $\gamma$ ) (50). CB1 and CB2 are expressed on MCs (51) and initiate a series of signal transduction events that converge at the transcriptional level to regulate cell migration and production of cytokines and chemokines (52, 53). Acting in concert with GPR55, CB2 mediates signals inhibiting MC degranulation and cytokine synthesis (54). Described anti-fibrotic effects of cannabinoid receptors in different MC-related disease models (55, 56) together with the recently deciphered crystal structure of CB1 and CB2 (57, 58) will allow development of selective agonists and their implementation in novel therapeutic concepts for allergic diseases.

## ALLERGY-ASSOCIATED IMMUNOMODULATORY LIPIDS ACT ON MAST CELLS

One would expect that allergen-associated lipids of plants or bacterial origin preferentially affect epithelial cells. Interaction of lipids with MCs might rather be possible in tissues with a damaged barrier (mainly by proteolytic activity of allergens) or indirectly in individuals showing previous sensitization

**TABLE 1** | Lipid categories and examples of lipids affecting MC reactivity.

Lipid category	Schematic structure	Examples of lipids with effects on MC reactivity	References
Fatty acyls	 $\alpha$ -Linolenic acid	Fatty acids, Omega 3, and 6 polyunsaturated fatty acids PG, TX, LT, LX AEA	(10–13) (14–16) (17)
Glycerolipids	 Triglyceride	2-AG	(17)
Glycerophospholipids	 Phosphatidylethanolamine	PC, PE, PI, PS, PAF	(18–20)
Sphingolipids	 Sphingomyelin	Ceramide C1P, S1P	(21) (22, 23)
Sterol lipids	 Cholesterol	Cholesterol Steroids Vitamin D <sub>3</sub>	(24–27) (28) (29, 30)
Prenol lipids	 Vitamin A	Carotenoids Vitamin E	(11) (31)
Saccharolipids	 Lipid A -disaccharide-1-phosphate	LPS	(32, 33)
Polyketides	 Griseorhodin A	Antibiotics Flavonoides	(34) (11)

<http://www.lipidmaps.org> is a source for structure of lipids. TX, thromboxane; PI, phosphatidylinositol.

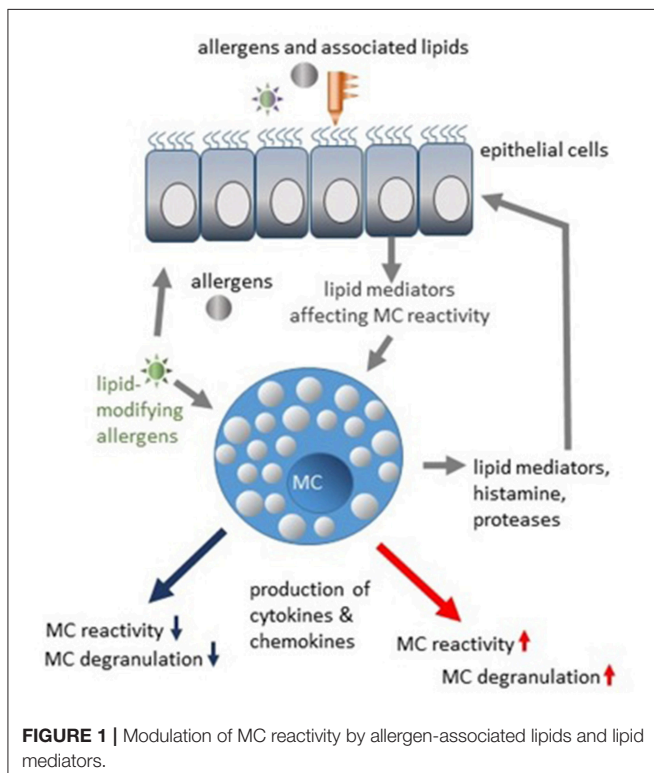
and presence of specific IgE and active transport of IgE-antigen complexes containing lipids. MCs are regulated by lipids associated with different allergens, as extensively reviewed elsewhere (59, 60). Interestingly, epithelial cells from healthy donors sense allergens differently than epithelial cells from allergic patients (61). Therefore, enhanced reactivity of MCs could be the result of a combined action of allergen-lipid complexes and pro-allergic inflammatory mediators produced by epithelial cells (**Figure 1**). Degranulation of human lung MCs has been shown to be inhibited in coculture with bronchial epithelial cells (62), substantiating the hypothesis that epithelial cells can provide the inhibitory signals to MCs as well. Attractive candidates potentially limiting MC-reactivity are specialized pro-resolving mediators (SPMs) crucial for the resolution of inflammatory processes (63, 64). Four classes of SPMs have been characterized so far. Lipoxins (LX) are biosynthetic products of arachidonic acid. Resolvins, protectins, and maresins are products of eicosapentaenoic acid (EPA), docosapentaenoic acid (n-3DPA) or docosahexaenoic acid (DHA) (64). The epithelial cell-derived resolvins D1, D2, and lipoxin A4 have been found to suppress IgE-mediated histamine release from MCs via G-protein-coupled receptors (65). Furthermore, airway inflammation, mucus production, and airway hyperresponsiveness *in vivo* as well as MC degranulation and cytokine release were decreased by lipoxin B4 application (16), indicating therapeutic potential of pro-resolving lipid mediators in regulation of MC reactivity. Whether SPMs could be produced by MCs themselves, is unknown.

One major class of allergen-containing particles represent plant pollens, where pollen grains are coated with different lipids

essential for plant fertilization (66). By interacting with immune cells and epithelial cells, pollen lipids may play an important role in immunoregulation. Two classes of pollen-associated lipid mediators (PALMs) have been described so far, namely LTB<sub>4</sub>-like mediators, which are monooxygenated derivatives of linoleic acid, and phytoprostanes generated from  $\alpha$ -linolenic acid in response to oxidative stress (67). Effects of PALMs on MC degranulation have been reported for aqueous pollen extracts (APE) derived from birch pollen and for APE from *Ambrosia artemisiifolia* (68). Here, degranulation was induced in skin MCs of C57BL/6 mice by intradermal injection of APE in the absence of specific IgE. It is not known whether MC degranulation can be induced by APE themselves in the presence of an intact skin barrier. In experiments with RBL cells, it has been shown that *Ambrosia* pollen extract induces histamine release by a ROS-dependent mechanisms, but not  $\beta$ -hexosaminidase release (69). In experiments with mountain cedar (*Juniperus ashei*) pollen extract, release of both serotonin and  $\beta$ -hexosaminidase was induced in RBL cells in an IgE-independent, but ROS-dependent manner. Added to suboptimal IgE/AG concentrations, pollen extracts enhanced degranulation of RBL cells (70), although lipid components in particular extracts were not analyzed. Interestingly, persistent contact with grass pollen in early childhood has been found to represent one of various allergy-protective factors (71). However, whether lipids are essential for tolerance induction and whether MCs are directly involved in tolerance development remains to be investigated.

## ALLERGENS INDUCE CHANGES IN MAST CELL LIPID COMPOSITION

Interaction of honeybee venom phospholipase A2 (PLA2) with membrane lipids is an example how allergen-induced modification of lipids could tune MC reactivity. Insect venom, particularly *Hymenoptera* venoms, induces a pronounced Th2 response by coopting evolutionary conserved immunological and neurological mechanisms (3, 72). A mixture of different substances, including enzymes, toxic peptides, lipids, and biogenic amines, is transported into the skin by the insect sting and induces a local inflammatory reaction, leading to sensitization and IgE production. Phospholipase A2 is one of the two major honeybee (*Apis mellifera*) venom allergens (73, 74). Cleaving cell membrane phosphodiacylglycerides, PLA2 induces the release of lysophospholipids, particularly lysophosphatidylcholine (LPC), together with fatty acids. This local lipid remodeling can affect MC reactivity *per se* and lead to MC degranulation (75, 76) (**Figure 1**). The stimulatory effect on MCs is absent if the enzymatically inactive form of PLA2 is used (77). PLA2 enzymatic activity is also required to induce a Th2 response (78). Generated neoantigens in the skin are presented by the CD1a molecules of antigen-presenting cells (APCs) and then induce a polyclonal T cell response (79). Interestingly, the stimulatory effects of PLA2 were observed only in the presence of lipids, either venom- or host-derived, indicating that lipid and protein components act in concert to induce a T cell response (79). PLA2 activity has also been detected





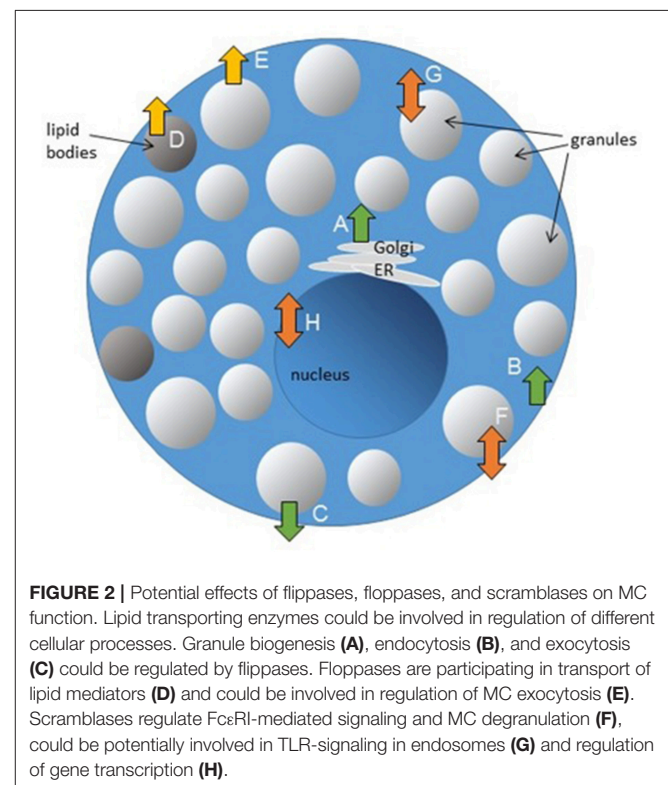
in house dust mite extracts (80), indicating that generation of lysophospholipids could be a part of allergic sensitization program. Moreover, an interaction between MCs and dendritic cells (DCs) has been demonstrated in contact hypersensitivity models (81, 82), where MCs were “cross-dressed” with DC MHC class II complexes. How the local changes of lipid composition, induced by e.g., PLA2 activity, modulate the MC-DC interaction and which functional consequences this would have for the T cell response in allergic settings remains to be further elucidated.

## MEMBRANE LIPID ORGANIZING ENZYMES ARE TARGETS TO MODULATE MAST CELL ACTIVATION

Organization of membrane lipids plays an important role in regulation of MC degranulation. The inner leaflet, facing the inside of the cell, contains negatively charged aminophospholipids, and phosphatidylethanolamine (PE). The outer leaflet, facing the outside environment, contains phosphatidylcholine (PC) and sphingomyelin. Asymmetric distribution of phospholipids in the plasma membrane plays an essential role in regulation of MC exocytosis (83). Interestingly, one of the earliest events in MC degranulation is a redistribution of phosphatidylinositol 4,5-bisphosphate [PtdIns(4,5)P<sub>2</sub>] disappearing from the plasma membrane within seconds after stimulation (84). Furthermore, MC degranulation is associated with reversible phosphatidylserine (PS) translocation to the plasma membrane (85), in contrast to various other cell types, in which the PS translocation represents an apoptotic “eat-me” signal. PS exposure can implicate endocytosis, acquisition of membrane curvature, regulation of transmembrane proteins, interactions with cytoskeletal elements as well as involvement in PS signaling (19). Lipid transporting phospholipid scramblase 1 (PLSCR1), floppase ABCA1 or transmembrane protein TMEM16F are the candidates responsible for PS translocation (19, 86). Interestingly, PS translocation in MCs could be induced not only by FcεRI-mediated activation. Crosslinking of glycosylphosphatidylinositol-anchored proteins by specific antibodies or lectins also induce PS externalization, using probably a different Ca<sup>2+</sup>-independent mechanism (87). It seems that the context in which MCs recognize PS is important, since free PS and lyso-PS enhance FcεRI-mediated degranulation (88) and phosphatidylserine-specific phospholipase A1, released e.g., by activated platelets, generates lyso-PS and strongly enhances MC histamine release (75). However, recognition of PS on the surface of apoptotic cells by the inhibitory receptor CD300a leads to a downregulation of inflammatory cytokine and chemokine production (89). Also, rodent MCs express α-galactosyl derivatives of the ganglioside GD1b (90). Antibodies recognizing this ganglioside inhibit degranulation and histamine release by modulating FcεRI endocytosis (90, 91) but in contrast, are also able to promote release of cytokines and lipid mediators (92).

Lipid content and distribution in membranes are regulated by different enzymes. Three types of phospholipid transportation enzymes are responsible for maintenance of the phospholipid asymmetry in membranes: (1) flippases that catalyze translocations of phospholipids between membrane leaflets in an energy-dependent or independent manner, primarily from the external to the internal leaflet, (2) floppases that transport lipids from the cytoplasmic leaflet to the external membrane leaflet, and (3) scramblases that move lipids between the two leaflets [as reviewed in Pomorski and Menon (93)]. Potential effects of flippases, floppases, and scramblases on MC function are outlined in Figure 2.

Flippases are members of the P4-type ATPase family with a similar structure containing 10 transmembrane domains, an actuator domain, a phosphorylation domain, and a nucleotide-binding domain associating with an accessory subunit Cdc50, forming a heterodimeric complex. In mammals, 14 different P4-ATPases have been identified as heterodimers consisting of a catalytic subunit in association with one member of the Cdc50 family (94). Many P4-ATPases are ubiquitously expressed and have been implicated in different metabolic diseases (95). P4-ATPases are also involved in the phospholipid transport between different subcellular compartments and are responsible for maintenance of phospholipid asymmetry in different cell types. Lipid transport by P4-ATPases is lipid-specific, head group-, and backbone-dependent (96). P4-ATPases regulate vesicular trafficking and the bidirectional vesicular transport between



the Golgi complex and early endosomes, but also vesicle biogenesis by enriching specific phospholipids in yeast cells, formation of post-Golgi vesicles in plant cells, as well as maintenance of membrane integrity and secretory processes (95, 97). Involvement of this class of lipid transporters in MC granule biogenesis and exocytosis is obvious. Genetic models with MC-specific P4-ATPase inactivation/overexpression could help to better understand essential regulatory steps in granule development, maturation and degranulation of MCs. Improvement of the knowledge on MC granule organization will also help to develop new strategies to interfere with MC degranulation.

Lipid transporters, shipping lipids from the inner membrane leaflet to the outer leaflet, are ATP-binding cassette (ABC) proteins, originally identified as multidrug resistance gene products in tumor cells. ABC proteins are encoded as single polypeptides, which can form homo- or heterodimers, contain an ATP-binding site, a nucleotide-binding domain and up to 17 transmembrane domains (98). Leukotriene C4 was the first lipid mediator described, transported by ABCC1/MRP1 (99). Different other lipid mediators such as prostaglandin A2 (PGA2) and 15-deoxy- $\Delta^{12,14}$  PGJ2, lysophosphatidylinositol (LPI) are also transported by specific ABC proteins (100, 101). In MCs with downregulated ABCC1/MRP1 expression, transport of S1P was strongly reduced, indicating an ABC-dependent regulation of MC chemotaxis and migration (102). How the lipid transport can be modulated by targeting other ABC proteins and how this will affect MC function is currently unknown. Mutations of ABC lipid transporters are responsible for several human diseases, such as neonatal surfactant deficiency (ABCA3 mutation) or Tangier disease (ABCA1 mutation), characterized by decreased removal of cholesterol from peripheral tissues (103).

Scramblases are structurally related proteins, containing a DNA-binding domain, a palmitoylation motif, a  $\text{Ca}^{2+}$ -binding motif, transmembrane domains and a nuclear localization signal. Located in the plasma membrane, scramblases are involved in the  $\text{Ca}^{2+}$ -dependent distribution of phospholipids (scrambling) (104). In 2008, the group of Benhamou identified phospholipid scramblase 1 (PLSCR1) as specific regulator of Fc $\epsilon$ RI signaling (105). Initially, PLSCR1 was only marked responsible for the rapid redistribution of phospholipids between two leaflets of the plasma membrane after cell activation or apoptosis, leading to the disruption of their asymmetric distribution (106–108). In the meantime, however, it is known that PLSCR1 serves numerous functions beyond the redistribution of phospholipids, such as the regulation of cell proliferation, differentiation, apoptosis, and tumor development (109–112). PLSCR1 requires palmitoylation to be stabilized at the plasma membrane. In the absence of palmitoylation, it is found in the nucleus, where it can bind DNA and activate the transcription of the inositol phosphate-3 (IP3) receptor (113, 114). When palmitoylated and localized at the plasma membrane, it participates in the epidermal growth factor signaling (115) by amplifying activation of the tyrosine kinase Src (116).

Knock-down of PLSCR1 in RBL-2H3 cells significantly impaired Fc $\epsilon$ RI-mediated degranulation and release of vascular

endothelial growth factor (105). Earlier, Pastorelli had already observed that phosphorylation of PLSCR1 is increased following the engagement of Fc $\epsilon$ RI in RBL-2H3 cells (117). Tyrosine phosphorylation of PLSCR1 following Fc $\epsilon$ RI aggregation relies on Lyn and Syk tyrosine kinases and partially also on calcium mobilization. In contrast, Fyn signaling negatively regulated PLSCR1 phosphorylation, suggesting a complex modulation of Fc $\epsilon$ RI-dependent MC activation by PLSCR1 (105, 118). *In vivo* studies using *Plscr1*<sup>-/-</sup> mice showed reduced Fc $\epsilon$ RI-dependent passive systemic anaphylaxis and serum histamine levels compared to wild-type mice (119), demonstrating the involvement of PLSCR1 in IgE-mediated anaphylaxis without affecting the phenotype or tissue distribution of resting MCs. Surprisingly, anaphylactic reactions induced by direct injection of histamine were slightly increased in *Plscr1*<sup>-/-</sup> animals, indicating that PLSCR1 also counter-regulates IgE-dependent anaphylaxis at later stages.

The modulatory ability of PLSCR1, allowing increased as well as decreased biological responses, might serve to sophisticatedly regulate inflammation, host defense, tissue remodeling and homeostasis and provide a rationale for exploiting PLSCR1 as therapeutic target in allergies (119, 120). Interestingly, in plasmacytoid DCs, PLSCR1 interacts with TLR9, and regulates the type I IFN response by modulating endosomal trafficking of TLR9 (121). Also, scramblase 2 (PLSCR2) has been found to be involved in the antiviral response. PLSCR2 binds to STAT3 and in this way also participates in downregulating the type I interferon response (122). Whether comparable effects will be observed in MCs and whether the antiviral response of MCs is compromised in the absence of scramblases remains an open question for future investigations. Mice deficient for scramblase 3 developed metabolic syndrome and lipid accumulation in abdominal fat pads (123).

Modulation of MC degranulation by affecting the lipid composition of the cell membrane or the enzyme activity modulating the lipid distribution of the membrane are potential emerging therapeutic strategies for the treatment of allergic diseases.

## CONCLUSION AND PERSPECTIVES

The rapidly emerging field defining modulation of MC reactivity by lipids, in addition to proteins, reveals novel and unprecedented targets, which may serve to preclude MC effects in allergic reactions. Active substances secreted by MCs have already been studied extensively, but data on the overall lipid composition of MCs and on stimulus-specific as well as sub-cell type-specific lipidomic data are still missing. Direct effects of immunomodulatory lipids on MC degranulation, changes in MC lipid composition induced by allergens themselves and changes in lipid transport and metabolism in MCs have not yet been comprehensively investigated. Furthermore, current studies investigating MC lipids are often limited by use of non-physiologic conditions or narrow restriction of the lipids that were analyzed. Therefore, addition of modern lipidomic approaches to the toolbox of immunology and cell

biology is crucial. Hereby, the added knowledge of lipid production and regulation together with deep understanding of MC biology will help find new mechanisms regulating MC responses. Coupled with this, an in-depth knowledge will be considerably advantageous for patients with anaphylaxis, asthma, allergic rhinitis, eczema, urticaria, mastocytosis, and other allergic diseases.

## AUTHOR CONTRIBUTIONS

PH, SN-D, JH, KH, and ZO wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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