Review

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Review

Potential Role of Moesin in Regulating Mast Cell Secretion

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Abstract: Mast cells play a critical role in allergies and inflammation via secretion of numerous vasoactive, pro-inflammatory and neuro-sensitizing mediators. Secretion may utilize different modes that involve the cytoskeleton, but our understanding of the molecular mechanisms regulating secretion is still not well understood. We previously showed that the ability of the so called mast cell "stabilizer" disodium cromoglycate (cromolyn) to inhibit secretion from rat mast cells closely paralleled the phosphorylation of a 78 kDa protein, and subsequently showed this protein to be moesin, a member of the Ezrin/Radixin/Moesin (ERM) family of proteins, which are involved in linking cell surface-initiated signaling to the actin cytoskeleton. Unlike phosphorylation on the C-terminus Thr558 associated with activation of ERMs, including secretion from macrophages and platelets, we showed that phosphorylation of moesin during inhibition of secretion was on the N-terminal Ser56/74 and Thr66 residues. This phosphorylation pattern could lock moesin in its inactive state and remain inaccessible to bind to the Soluble NSF attachment protein receptors (SNAREs) and synaptosomal associated proteins (SNAPs). Using Confocal microscopic imaging, we showed moesin to colocalize with actin and cluster around secretory granules during inhibition of secretion, In conclusion, the phosphorylation pattern and localization of moesin may be important in the regulation of mast cell secretion and could be targeted for the development of effective inhibitors of secretion from mast cells.

Keywords: ERMs; flavonoids; luteolin; mast cells; mediators; moesin; phosphorylation; secretion; SNAREs; SNAPs; tryptase

1. Introduction

Mast cells are specialized hemopoietic cells that play an important role in health,1 and in allergies,2-12 but also in innate and in adaptive immune processes,13-16 antigen presentation,16, 17 regulation of T-cell responses,18-20 autoimmunity,21 and inflammation,10, 22-25 in response to allergic and immunologic,4, 26, 27 but also non-allergic stress and toxic stimuli.10, 28 Mast cells are increased in number and are more reactive in mastocytosis26 and Mast Cell Activation syndrome (MCAS),26, 29, 30 but can also participate other disorders,4, 10, 31-33 including neurotrauma, neuroinflammatory and neurodegenerative diseases.34-36

Mast cells are located in tissues at the interface with the external environment37 such as eyes, nose, lungs, skin and gastrointestinal tract. However, perivascular mast cells also sense the blood vessel lumen by extending filopodia through endothelial gaps and bind circulating immunoglobulin E (IgE).38 Mast cells are well known for their involvement in allergic and anaphylactic reactions via activation of the high-affinity surface receptor for IgE (FcεRI). Multivalent allergen binding leads to aggregation of FcεRI and influx of calcium ions thus initiating a cascade of downstream events that involve phosphorylation of phosphatidyl inositol (IP3) and various Tyr kinases.39-42 In addition to allergens, mast cells are also stimulated by a variety of triggers that include drugs, foods, pathogens, and "danger signals,"26 as well as certain neuropeptides especially substance P (SP)43 via activation of their high-affinity receptors. Mast cells are also stimulated/activated by several cytokines, chemokines, and hormones such as corticotropin-releasing hormone (CRH), toxins and extreme external environmental changes.23, 36, 44, 45

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Upon stimulation, mast cells secrete multiple biologically active mediators,46 some of which are preformed and stored in as many as 1,000 secretory granules per cell such as β-hexosaminidase (β-hex), heparin, histamine, tumor necrosis factor (TNF) and the serine proteases chymase and tryptase tryptase through rapid (1-5 min) degranulation by exocytosis.47 Histamine and tryptase are the main mediators associated with mast cells.48 Chymase is found in all mast cells, but unlike mucosal mast cells (MMCs) that contain only chymase, connective tissue mast cells (CTMCs) contain both chymase and tryptase. Even though these proteases are considered to be stored in the same secretory granules, there is evidence that this may not be necessarily true. For instance, serum tryptase was not elevated in many patients with MCAS28 or in cutaneous mastocytosis.49 In one paper, it was shown that IgE-mediated degranulation of primary murine MMCs and CTMCs released phenotypically different extracellular vesicle (EV) populations depending on the stimulus.50 In particular, unstimulated mast cells constitutively released CD9+ EVs, while degranulation was accompanied by the release of CD63+ EVs that contained different proteases.50

Mast cells also release newly-synthesized phospholipid products such as prostaglandin D2 (PGD2) and leukotrienes (LTs),51-53 as well as numerous *de novo* synthesized protein mediators 6-24 hours after stimulation such as interleukins,54 including interleukin-1beta (IL-1β), 55 IL-6,45, 56 IL-31, 57 IL-3355 and TNF.43

Mast cells can secrete their numerous mediators25, 47, 58 utilizing different signaling11, 59-62 and secretory60, 63 64 pathways sometimes referred to as the "secretome".65 The secretory pathways include degranulation by exocytosis, compound exocytosis, piecemeal degranulation, transgranulation, directed degranulation, vesicular (differential) release of mediators, extracellular microvesicles (exosomes), nanotubules.66 and antibody-dependent "immunologic synapses for dedicated secretion67, 68 (Table 1). The term "secretion" is used in this review to include both degranulation by exocytosis, which is the main means of secretion of granule-stored mediators,69 as well as differential release via which chemokines and cytokines are released without degranulation.59 For instance, we first reported that serotonin,45, 52, 56 and later vascular endothelial growth factor (VEGF),70 and IL-6 45, 56 could be secreted from mast cells without degranulation and without the release of histamine or tryptase.59 We had also reported that mast cells can release the content of individual secretory granules71 or individual mediators without degranulation.52 This process was distinct from "piece-meal degranulation",72 granule-associated vesicle transport63 or the release of extracellular vesicles.67, 73-78

Table 1. Different Modes of Secretion of Mediators from Mast Cells.

Degranulation (exocytosis)
Compound exocytosis
Piece meal degranulation
Transgranulation
Directed degranulation
Vesicular (differential) release of mediators
Extracellular microvesicles (exosomes)
Nanotubules
Immunologic synapses

Moreover, mast cell mediators could have autocrine actions affecting the expression of receptors or the overall reactivity of mast cells. For instance, mast cells can release the "alarmin" IL-33, themselves.55 IL-33 then stimulated mast cells via activation of its own specific surface receptor ST2 and significantly increased the ability of substance P (SP) to secrete VEGF,79, 80 IL-31, 57 TNF43 and IL-1β.55 Mast cell-derived IL-1β or histamine further stimulated release of IL-1β from macrophages.81 IL-1β could, in turn, stimulate mast cells to release IL-6, which was shown to stimulate mast cell proliferation.82 The presence of the D816V-KIT mutation in mast cells was associated with constitutive release of IL-6.83 Serum levels of IL-6 were reported to be elevated in mastocytosis84-86 and correlated with disease severity. Mast cells could also undergo directional mast cell degranulation and secretion of TNF and possibly other pro-inflammatory mediators into the bloodstream.87 It is also important to note that mast cells exhibit different phenotypes including

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expression of different receptors depending on the tissue microenvironment.88 Moreover, different receptors may interact and increase mast cell reactivity,89 as shown for FcεRI and MRGPRX2, which were reported to have additive effect in stimulating degranulation in human skin mast cells.90

IL-33 increased the expression of the SP receptor neurokinin-1 (NK-1), while SP increased expression of the IL-33 receptor ST2.55 SP also induced expression of the receptor CRHR-1 for the key stress hormone CRH in human mast cells.91 Instead, SP downregulated expression of FcεRI in human mast cells.92 CRH stimulated mast cells to release VEGF without degranulation, an action that was augmented by the peptide neurotensin (NT);93 during this process, CRH stimulated the expression of the NT receptor NT3, while NT stimulated the expression of CRHR-1.94 These findings could help explain why many atopic patients worsen dramatically after a major stressful episode.95, 96.

Mast cell-derived mediators could also induce epigenetic effects as shown for tryptase, which could catalyze histone clipping97 and could regulate modification of histones in mast cell leukemia cells.98 Expression of Ten-eleven translocation-2 (TET2), an epigenetic regulator, was induced in response to activation of mast cells.99, 100 Hence, mast cells are very dynamic cells that respond not only to external but also to innate stimuli. Such findings have prompted the re-evaluation of the secretory processes and their regulation in mast cells.101

Our understanding of the regulation of mediator release via these different modes of secretion and its regulation is still poorly understood. Even though the stimulus-response coupling pathway has been well delineated for activation of the high-affinity surface receptor for IgE (FcεRI),42, 102, 103 and more recently of the low-affinity receptor for cationic peptides, Mas-Related G Protein-Coupled Receptor-X2 (MRGPRX2),104-108 there is still a lack of understanding of the molecular events regulating secretion, whether by degranulation, selective release of mediators or any other mode of secretion (Table 1). The mode and extent of mast cell responsiveness ultimately depend on the interplay between stimulatory and inhibitory signaling pathways, such as CD300109, 110 and Singlets,111 especially Siglec-7,112 and the β subunit of FcεRI (FcεRIβ).113

In spite of the advances briefly outlined above, there is still no effective inhibitor of mediator secretion from mast cells. Antihistamines interfere with histamine binding to its receptors after it has been secreted. There has been considerable progress in developing drugs that block tyrosine kinases involved in mast cell proliferation.114 As a result, our understanding of mast cell stimulation especially by non-IgE triggers remains poor and there are still no clinically effective inhibitors of mast cell activation and inflammatory mediator release.

2. Ezrin, Radixin, Moesin (ERM) Family of Proteins

Ezrin, radixin and moesin (ERMs) are fairly homologous proteins (73% amino acid identity) that link the actin cytoskeleton to the cytoplasmic tail of transmembrane proteins in the plasma membrane thus regulating the formation of F-actin-based structures.115-120 ERMs localize to cell surface protrusions such as microvilli, filopodia and cell–cell junctions ERMs are critical for signal transduction from the cell surface into the cell. Given the high degree of homology and their co-expression to various degrees in many cell types, overlapping or even compensatory functions have been proposed.

Ezrin was named after Ezra Cornell University where it was first isolated from microvilli in chicken intestinal epithelial cells, while radixin (from the Latin meaning root) was isolated from the adherens junctions of rat liver hepatocytes. Moesin (membrane-organizing extension spike protein) was isolated from smooth muscle cells of the bovine uterus. ERMs contain two functional domains connected through a long α-helix region (Fig. 1A): the N-terminal FERM (band 4.1 protein-ERM) domain, which is critical for the function of the ERMs, and the C-terminal ERM association domain (C-ERMAD). The FERM domain is composed of three subdomains (F1, a ubiquitin-like domain; F2, with four α-helices; and F3, a pleckstrin homology domain). The FERM domain and the C-ERMAD can bind each other in a head-to-tail manner, leading to a closed/inactive conformation (Fig. 1B).

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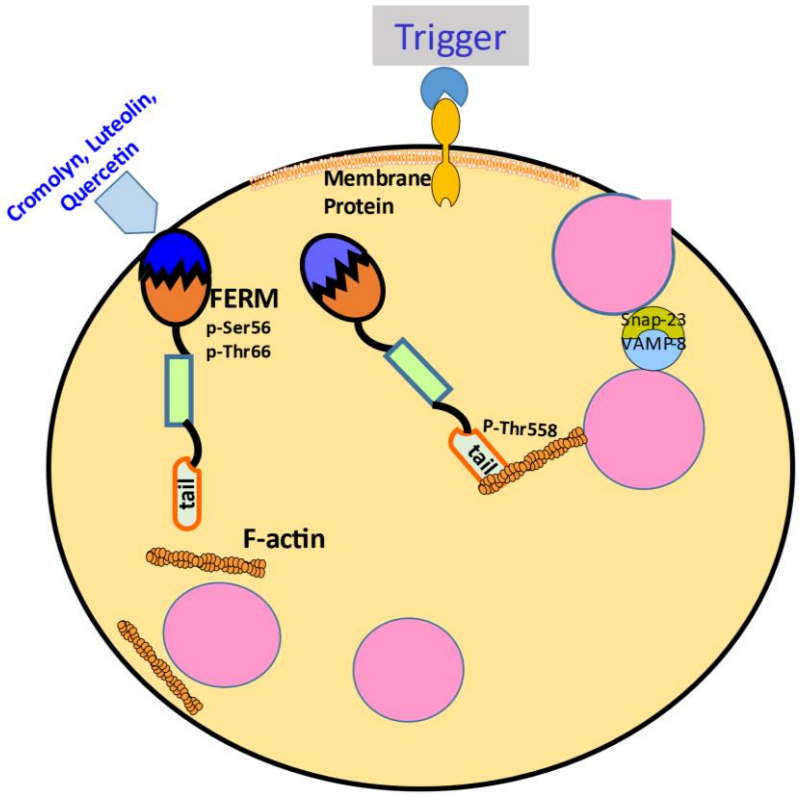

Figure 1. Diagrammatic representation of how differential phosphorylation of moesin could regulate secretion from mast cells. Phosphorylation of moesin at Thr558 in response to triggers opens up binding sites permitting granules to travel to the cell surface and secrete granule-stored mediators via degranulation. In contrast, phosphorylation of moesin at Ser56/Thr66 by cromolyn or flavonoids changes the conformational structure of moesin so that Ser558 is no longer accessible to bind to actin thus preventing secretion.

The release of the C-ERMAD from the FERM domain is necessary for the activation of ERMs, unmasking their F-actin- and PM-binding sites. Activation of ERMs occurs first by phosphatidylinositol 4,5-bisphosphate (PIP2) binding to the N-terminus and changing the 3-D structure exposing a C-terminal Threonine (Thr567 in ezrin, Thr564 in radixin and **Thr558 in moesin**) for phosphorylation116, 121 by the Rho family of GTPases (RhoA/Rac/Cdc42). This step transitions ERMs from a closed (inactive, Fig. B) to an open (active, Fig. 1A) conformation122 that exposes the C-terminal F-actin binding domain that cross-links plasma membrane proteins with actin filaments (Fig. 2).116, 119-122

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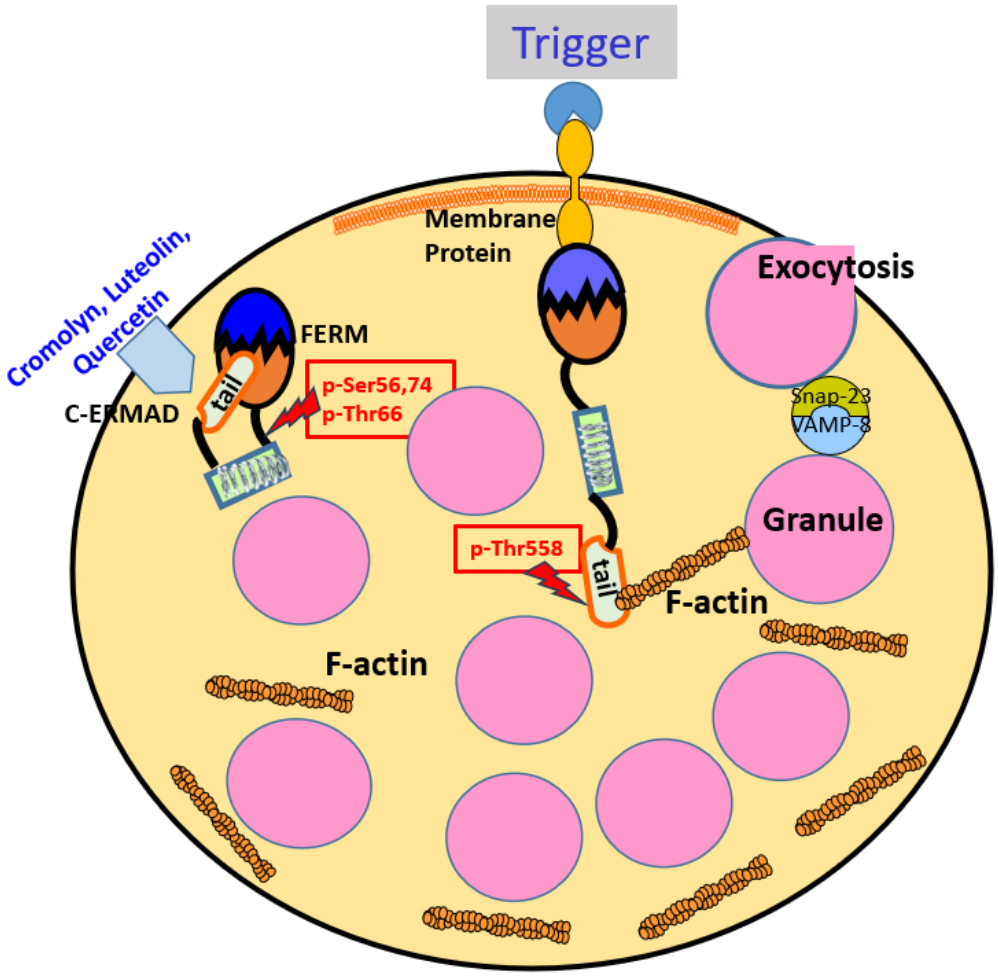

Figure 2. Moesin in Mast Cell Secretion.

3. Moesin in mast cells

The expression of particular ERM members varies among different cells. Moesin is mainly expressed in endothelial cells, ezrin in intestinal epithelial cells and radixin in hepatocytes. However, moesin is the most abundant ERM in leukocytes, whereas ezrin is less expressed and radixin is nearly absent;118 we found that the same was also true for mast cells.

Mast cells, like any other secretory cell, require the actin cytoskeleton123 that is necessary for signal-transduction and movement of secretory granules or vesicles destined for secretion to the cell surface. For instance, aggregation of IgE bound to FcεRI by a multivalent antigen stimulates mast cell secretion and rapidly depolymerizes actin filaments, with the actin-severing protein cofilin being dephosphorylated several minutes after stimulation.124In contrast, disaggregation of IgE terminates degranulation mediated by dephosphorylation of Syk associated with a decrease in intracellular Ca2+ concentration and rapid recovery of actin polymerization. Upon FcεRI stimulation, Dok-1(downstream of tyrosine kinase 1), undergoes Tyr phosphorylation, which negatively regulates Ras/Erk signaling and the subsequent secretion.125 Following FcεRI activation, Dok-1 is recruited to the plasma membrane, leading to Tyr phosphorylation. In contrast, phosphorylation of Dok-1 inhibited FcεRI-induced calcium influx and calcium-dependent disassembly of actin filaments, thus negatively regulating degranulation.125 It was previously shown that Rho GTPases regulate exocytosis and possibly secretory granule transport. One paper used live-cell imaging to analyze cytoskeleton assembly and secretory granule transport in real-time of mast cells or rat basophil cells (RBL-1) during antigen stimulation. This paper showed that granule transport to the cell periphery was coordinated by *de novo* microtubule formation and not F-actin since kinesore, which activates the microtubule motor kinesin-1 inhibited microtubule-granule association and significantly reduced degranulation.126 However, how F-actin or microtubules communicate with secretory granules (or

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vesicles) and the plasma membrane is still not well understood. Knockdown of the unconventional long-tailed myosin (MYO1F), which localizes with cortical F-actin by short hairpin RNA, reduced human mast cell degranulation stimulated by both IgE and MRGPRX2, and was accompanied by reduced reassembly of the cortical actin ring and fewer secretory granules localized close to the cell surface.127 Interestingly, MYO1F knockdown also resulted in fewer fissioned mitochondria and deficient mitochondria translocation to sites of degranulation by exocytosis.127 We had also shown that mitochondria fission accompanied secretion by degranulation, but not during secretion of *de novo* synthesized mediators from human mast cells stimulated by SP18 and also in skin biopsies from patients with atopic dermatitis.128 We further showed that stimulation of mast cells resulted in extracellular secretion of mitochondrial DNA (mtDNA) that acted as an "innate pathogen" and triggered an autoinflammatory response. Increased levels of mtDNA have been reported in patients with COVID-19,129-132 psoriasis,133 as well as in EVs from patients with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS)134 and from children with autism spectrum disorder (ASD), in both cases of which mtDNA activated cultured human microglia to secrete IL-1β.135

We had shown that the ability of the so called "mast cell stabilizer" disodium cromoglycate (cromolyn) to inhibit secretion from rat mast cells in response to the cationic Compound 48/80 (C48/80) closely paralleled the phosphorylation of a 78 kDa protein,136-138 on the ***N-terminal Ser56, Ser74 and Thr66*** residues (Fig. 1B).139 We subsequently cloned this protein from mast cells and showed it to be moesin,140 but we had called it ***Ma***st ***Ce***ll ***D***egranulati***o***n ***I***nhibitory ***A***gent=MACEDONIA.141 It is important to note that phosphorylation of at least the ***N-terminal Ser56/74 and Thr66 residues*** during inhibition is different than the well-known phosphorylation of C-ERMAD Thr558 associated with moesin activation, inhibition of mast cell secretion of histamine was associated with.139 In support of the involvement of additional phosphorylation sites than Thr558, there is evidence that at least in ezrin, Thr235 is phosphorylated by cyclin-dependent kinase 5 (CDK5) and cooperates with Thr576 for its full activation.142

Using Confocal microscopy and ultra cryo-immuno-electron microscopy to preserve the antigenicity of ERMs, we had shown that mast cells contain almost exclusively moesin, (with a small amount of ezrin), which was critically localized primarily at the plasma membrane and filopodia, with less around secretory granules; we further showed that cromolyn induced clustering of moesin around secretory granules.140 We hypothesized that conformational changes of moesin, regulated by phosphorylation/dephosphorylation, could possibly regulate mast cell secretion via positional rearrangements with respect to the membrane/cytoskeleton.140 We further hypothesized that moesin could, in fact, serve a dual function depending on its phosphorylation pattern that occurs after a trigger or an inhibitor interacts with the cell surface.143 In other words, moesin phosphorylation at C-terminal Thr558 would switch moesin to its active form (Fig. 1A) and permit mast secretory granules to move to the surface, fuse with the plasma membrane and undergo exocytosis (Fig. 2). In contrast, phosphorylation of N-terminal Ser/Thr sites would switch moesin to its inactive state (Fig. 1B) resulting in either: (a) prevention of phosphorylation of Thr558 and moesin activation, (b) interaction with secretory granules preventing them from moving to the cell surface or (c) affecting the structure of the cell cortex and block secretion indirectly (Fig. 2). However, it remains unknown how phosphorylation of moesin at different sites affects secretion from mast cells in response to different triggers, and how phosphorylation at the N-terminal sites mechanistically leads to inhibition of mast cell secretion. Moreover, it is not presently known if phosphorylation of moesin may affect modes of secretion other than degranulation by exocytosis. One paper identified a number of ser/thr phosphorylated proteins in activated mast cells, including moesin, but these were involved in different processes such as metabolism and cell structure.144 Even though ezrin has been mostly discussed for its involvement in cancer,145 it is not known if ezrin could compensate for moesin should the latter be absent or "incapacitated" in mast cells. In fact, ezrin, has been implicated in asthma.146 **Phosphorylation of ezrin at Thr567 was associated with trophoblast motility.147**

Interestingly, moesin knock-out mice were shown to have lymphopenia,148 but mast cell numbers were apparently intact; however, the authors did not investigate mast cell secretion.148 One X-linked moesin-associated immunodeficiency (X-MAID) has been identified and is characterized by a primary immunodeficiency associated with severe lymphopenia leading to recurrent infections. X-MAID is caused by a single point mutation leading to a R171W amino acid change in moesin

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(moesinR171W).149 In fact, a mouse model with global expression of moesinR171W exhibited lymphopenia, but was still characterized by systemic inflammation.149

Phosphorylation of moesin has also been studied in other secretory systems. Moesin was shown to be phosphorylated at Thr558 within seconds of thrombin-induced activation of platelets.150, 151 Instead, tyrosine phosphorylation of moesin was reported during the activation of platelets by arachidonic acid.152 These phosphorylation patterns are reversed by protein phosphatase 2C, which inactivates the F-actin binding site of activated platelets.153 Phosphorylation at Thr558 was also reported in activated RAW264.7 macrophages.154 ERM proteins have been shown to be involved in T-cell polarization and immune synapse formation.155 It is interesting that anti-moesin autoantibodies were isolated from patients with aplastic anemia156 and autoimmune vasculitis.157 However, their significance of these autoantibodies is not apparent nor is their potential presence in patients with allergies and inflammatory disorders.

4. SNAREs and SNAPs

One possible mechanism of how moesin may regulate mast cell secretion could involve the Soluble NSF attachment protein receptors (SNAREs) and synaptosomal associated proteins (SNAPs) discovered by Dr. J.E. Rothman, who was awarded the 2013 Nobel in Physiology and Medicine for delineating the principles for membrane fusion during secretory membrane fusion.158 The existence of distinct secretory vesicle calcium-sensitive proteins "snapping" with corresponding proteins on the plasma membrane during secretion of mast cells had actually been proposed much earlier by one of the authors (TCT) in his doctoral thesis examination at Yale University in 1974 with examiner being Dr. G. Palade who had just received the 1974 Nobel in Physiology and Medicine for his discovery that secreted proteins are carried from the endoplasmic reticulum (ER) to the cell surface in specialized compartments or transport vesicles.

SNAREs159-161 and synaptosomal associated protein of 23 kDa) (SNAP-23)162-167 have been shown to be involved in mast cell secretion (Fig. 2). In fact, there may be different mechanisms regulating exocytosis in mast cells168 and mast cell distinct secretory granule subsets may be regulated by different SNARE isoforms169 and different vesicle-associated membrane proteins (VAMPs), especially VAMP2- and VAMP8.170, 171

Mast cells express Munc18-2, which interacts with SNARE syntaxin 2 or 3, as well as Munc18-3, which interacts with syntaxin 4. Munc18-2 was localised to secretory granules, whereas Munc18-3 was found on the plasma membrane. Increased expression of Munc18-2 inhibited IgE-triggered exocytosis, while increased expression of Munc18-3 had no effect. Upon stimulation, Munc18-2 redistributed persisted on granules that were aligned along microtubules, but was excluded from F-actin ruffles, suggesting a role for Munc18-2 and the microtubule network in the regulation of secretion by degranulation in mast cells.172 In addition, a number of so-called 'adapters' have been reported to regulate secretion from mast cells by binding multiple signaling proteins and localizing them to specific cellular compartments. 40

It is of note that degranulation of different mast cell vesicle subsets was differentially and selectively regulated by various polyphenols via interfering with two SNARE complexes, Syn (syntaxin) 4/SNAP-23/VAMP2 and Syn4/SNAP23/VAMP8.173 Similarly, polyphenols were shown to interfere with "zippering" of SNARES in the neuron.174 The structure of the phenolic flavonol quercetin is somewhat similar to cromolyn,143 but is a more potent inhibitor than cromolyn.175 Quercetin inhibited rat mast cell degranulation,176, 177 possibly via inhibition of protein kinase C (PKC),138, 178 but it also induced phosphorylation of moesin.178 Quercetin also inhibited the release of pro-inflammatory cytokines,138 including IL-6,177 from cultured human mast cells. The quercetin-related flavone luteolin and the luteolin analogue tetramethoxyluteolin were even more potent inhibitors of both of degranulation,179 as well as of the release of TNF43 and IL-1β55 from human mast cells.

The ability of flavonoids to inhibit mast cell secretion via phosphorylation of moesin led to conjectures about design of more potent inhibitors.143

5. Neuroinflammation

Mast cells communicate with microglia180, 181 and can activate them181-184 via the release of mediators such as histamine185 and tryptase,186 leading to neuroinflammation.180, 182 Activation

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of mast cells and microglia in the brain187 could affect neurodevelopment,188 resulting in neuronal apoptosis,189 and lead to cognitive dysfunction.189 In fact activation of mast cells and microglia has been linked to the pathogenesis of autism spectrum disorder (ASD),190-194 **neurodegenerative diseases35, 195 and traumatic brain injury (TBI).24, 196 It is, therefore, of interest that moesin has been reported to be involved in the activation of microglia.197 Moreover, the moesin pseudogene 1 antisense (MSNP1AS) was shown to decrease the number and length of neurites, reduce neural viability and promote apoptosis via inhibition of moesin protein expression, while moesin improved social interactions and reduced repetitive behaviors in BTBR mice.198**

Moreover, one paper reported that ezrin, radixin and moesin had distinct roles of in maintaining the plasma membrane integrity and functions of the blood-brain barrier (BBB) transporters,199 which is important because mast cells can regulate the permeability of the BBB,200 disruption of which has been implicated in ASD,201 in Alzheimer's disease33 and in neuro-COVID.202 **In this context, it is relevant that** flavonoids could have anti-inflammatory34, 203-209 and neuroprotective effects,210 as well as reduce cognitive dysfunction,211-215 especially brain fog.216-218 In particular, luteolin inhibited both microglia219-221 and mast cells.222, 223

One formulation containing liposomal luteolin in olive pomace (fruit) oil (NeuroProtek®**)** resulted in significant improvement of children with ASD224 with a concomitant decrease in serum inflammatory markers.225 Other papers reported the beneficial action of luteolin in Long-COVID-associated brain fog.216, 226 and neurotrauma.227

6. Conclusions

The studies reviewed indicate that moesin phosphorylation and localization may be important in the regulation of mast cell-derived secretion of at least secretory granule-associated mediators such as histamine, TNF and tryptase.

It would be important to investigate the expression of total and phosphorylated moesin in human mast cells of different degrees of reactivity/types, such as the leukemic human mast cell line-1 (HMC-1), the Laboratory of allergic diseases-2 (LAD2) and LADR mast cells,228 as well as primary human umbilical cord blood-derived cultured mast cells (hCBMCs), mast cells developed from pluripotent stem cells,229-231 but also mast cells from a cutaneous mastocytosis or urticaria lesions. Other future studies should investigate whether the knockdown of moesin using small interfering ribonucleic acid (siRNA) would affect the extent of secretion or interfere with the ability of flavonoids to inhibit mast cell secretion. Additionally, studies should also investigate which specific sites are phosphorylated in response to triggers or inhibitors of either degranulation or differential release of select mediators using trypsin-digested moesin peptides analyzed by mass spectrometry and validated with site-specific phospho-antibodies and point mutant analysis.

It would be important to investigate the possible presence of some innate molecule or identify novel molecules that keep moesin in its inactive state, that could be targeted for the development of new effective anti-allergic and anti-inflammatory drugs.

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