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REVIEW

Mast cell activation: beyond histamine and tryptase

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ABSTRACT

Introduction: Mast cells are found in all tissues and express numerous surface receptors allowing them to sense and respond to allergic, autoimmune, environmental, neurohormonal, pathogenic and stress triggers. Stimulated mast cells are typically called 'activated' but the mechanisms involved and the mediators released can vary considerably. Mast cell activation diseases (MCADs) include primary, secondary and idiopathic conditions, especially mast cell activation syndrome (MCAS), but mast cells are activated in many other disorders making the diagnosis and treatment challenging.

Areas covered: Mast cells can release numerous biologically active mediators, some of which are prestored in secretory granules while others are newly synthesized and released without degranulation. Most of the emphasis has so far been on secretion of histamine and tryptase, which do not explain all the multisystemic symptoms experienced by patients with MCADs. As a result, drug development has focused on antiproliferative therapy or blocking the action of individual mediators and not on inhibitors of mast cell activation.

Expert opinion: Activated mast cells are involved in the pathogenesis of MCADs, but also in other disorders making appropriate diagnosis and treatment challenging. The definition of mast cell activation should be expanded beyond histamine and tryptase, with an emphasis on better detection and treatments.

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brain fog; comorbidities; diagnosis; inflammatory mediators; mast cells; mastocytosis; mechanism; treatment

1. Introduction

Mast cells [1–5] have existed for almost 500 million years [6,7] in many different species, including invertebrates and lower vertebrates (e.g. frogs, lizards, zebrafish) [8–10], suggesting that they served a critical role acting as multifunctional effector cells [11] or pluripotent 'immunoendocrine master players' [12].

Previous reviews have discussed the role of mast cells in health and disease not only in allergies [1,13–21], but also in immunity and inflammation [19,22–24]. In mammals, mast cells derive from hematopoietic CD34+ precursors [25–27], travel in the circulation as precursor cells, and express the surface antigens CD117 (KIT), a tyrosine kinase receptor which is the ligand for stem cell factor (SCF) [28]. In systemic mastocytosis, mast cell precursors also express CD3 and CD25. Mast cells are typically activated by allergens crosslinking specific immunoglobulin E (IgE) bound to its high-affinity surface Fc epsilon receptor 1 (FcεRI) [29,30]. IgE probably developed some 300 million years ago, and interesting that wild animals have much higher circulating IgE than humans, probably as a defense against parasites [31]. Interestingly, circulating basophils also express FcεRI and may have co-evolved with mast cells, but their pathophysiology is quite distinct [32,33]. Even though mature mast cells reside in the tissues, they probe the blood vessel lumen by extending filopodia through endothelial gaps, capturing circulating Ig [34,35]. Contrary to early research, fetal mast cells can bind maternal circulating IgE and contribute to postnatal allergic responses [36]. Surprisingly, prenatal stressful events increased umbilical cord blood IgE [35]. Mast cells can be stimulated by a plethora of other triggers indicating mast cell activation beyond IgE [37], and also the role of IgE beyond mast cells [38].

Mast cells are located in all tissues [39] perivascularly [26,40,41]. The chemokines C-C motif chemokine ligand 2 (CCL2) and CCL5/Regulated on Activation, Normal T Expressed and Secreted (RANTES) are potent chemoattractants for mast cells [42,43]. Mast cells 'mature' under the influence of local micro-environmental factors [44,45] such as interleukin-4 (IL-4), IL-6 and nerve growth factor (NGF) [46]. In fact, mast cells synthesize and release NGF, themselves [47]. Mast cells can assume different phenotypes [48], and have typically been divided based on their secretory granule content of serine proteases [49–51]. Mucosal mast cells (MMC) contain only chymase and connective tissue mast cells (CTMC) contain both chymase and tryptase [52]. However, it has never been shown conclusively that both these proteases are stored in the same secretory granules, and evidence had also indicated there may be more than one form of chymase [53]. Mast cell granules also store tissue remodeling enzymes, such as carboxypeptidase A3 (CPA3) and matrix metalloproteinases (MMPs) [54–57].

Mast cell subtypes can also be further distinguished based on the granule content of biogenic amines [58] and mucopolysaccharides such as chondroitin sulfate and heparin [1]. However, mast cell phenotyping may be modified the discovery of additional unique mast cell molecules [59,60] and expression of various surface receptors [61,62]. Figure 1 shows different models of release of mediators from mast cells that should be considered under the term 'activation.'

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Article highlights

- Mast cells have many different phenotypes that can change given the specific tissue microenvironment
- Mast cells synthesize, store and release hundreds of mediators in response to allergic, environmental, neuroimmune, stress and toxic triggers
- Release of histamine and tryptase are limited to degranulation, while other angiogenic, fibrotic, anti-inflammatory, proinflammatory and neurotoxic molecules can be released without degranulation
- Mast cell 'activation' should not be limited primarily to histamine and tryptase release
- Mast cell activation syndrome still requires serum tryptase elevation associated with an episode, but many more patients may qualify for mast cell activation, unspecified or for other mast cell activation disorder
- Activated mast cells are involved in many other conditions making diagnosis challenging and treatment difficult
- Treatment should focus on inhibition of mast cell activation, in addition to inhibiting the effects of selective mast cell mediators.

2. Mast cell activation disorders (MCADs)

Understandably, many reviews of mast cell activation diseases (MCAD)s focused on mastocytosis [39,63–67]. Briefly, MCADs can be divided as follows 1. Primary [e.g. mastocytosis, monoclonal mast cell activation disorder (MMAS)]. 2. Secondary [e.g. allergies, asthma, cancer, urticarias), and 3. Idiopathic [e,g, anaphylaxis, chronic spontaneous urticaria, mast cell activation syndrome (MCAS), mast cell activation, unspecified Sometimes, Primary MCADs are referred to as 'intrinsic' (1), while the Secondary MCADs as 'extrinsic.'

MCADs have different ICM1-CM diagnostic codes (Table 1) described in more detail by Valent et al. [68].

MCADs can be confusing [69–74] because there are over 30 other conditions in which activation of mast cells is suspected of being involved such as irritable bowel syndrome (IBS) [75] or autism spectrum disorder (ASD) [76] (Table 2). Moreover, there are also other conditions that mimic MCADs, but probably do not involve mast cells (Table 3). Moreover, there are conditions that are frequently comorbid with MCADs such as postural tachycardia syndrome (POTS) and hypermobile Ehlers-Danlos syndrome (EDS) [77–79] that together with MCAS have been called the 'triad' [80]. It was recently reported that dysautonomia was documented in most patients with MCAS [81]. Finally, many patients with MCADs are more sensitive to excipients such as additives, colorings and preservatives found in many foods, cosmetics, drugs and supplements [62].

The diagnosis of atopic diseases in general, and MCADs, in particular, depends on clinical history, the response to medications that can reduce mast cell-related symptoms, as well as the elevation of blood and urine biomarkers (Table 4) [82,83]. However, there are instances where mast cell involvement remains unrecognized as in patients with alpha-gal syndrome, which involves specific IgE to the oligosaccharide galactose-a-1,3-galactose (alpha-gal), and is often associated with tick bites, but is also found in mammal-derived ingredients commonly found in numerous cosmetics, drugs and supplements [84].

The definition of MCAS has generated considerable controversy [85–88]. There have been numerous papers presenting consensus criteria for MCAS, the most recent of which was by Dr. Gulen et al. that stressed the importance of incidence-associated elevation of serum tryptase levels and downplayed the significance of urine histamine and prostaglandin D2 (PGD2) metabolites [89]. These criteria translate to many fewer cases of idiopathic MCAS than suspected [90]. These criteria were subsequently slightly 'adjusted' to describe "a subset of patients with no underlying disease, no known trigger of mast cell activation and no specific criteria as of yet [68]. The original description of MCAS by Dr. Akin et al. [91] included elevated 24-hour urine 11β-$PGF_2α$, which was more

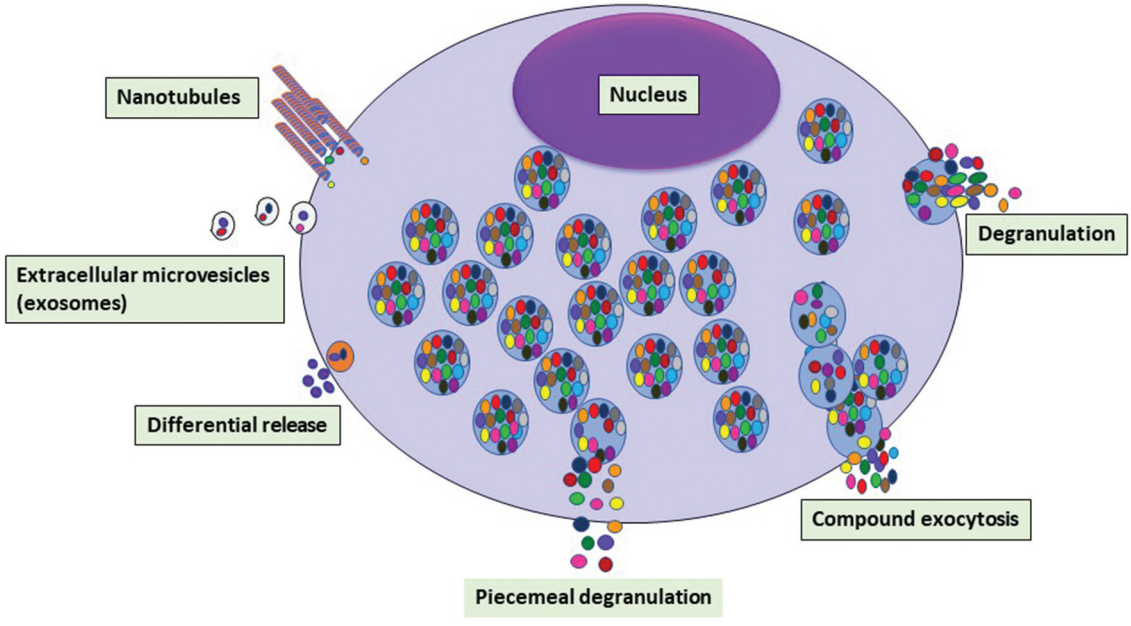

Figure 1. Schematic representation of different models of release of mediators from mast cells that should be considered under the term 'activation'.

Table 1. ICD10-CM diagnostic codes for MCADs (excluding mast cell neoplasms and mast cell leukemia).

C96.21 Aggressive systemic mastocytosis
D47.02 Systemic mastocytosis
D47.01 Cutaneous mastocytosis
D89.4 Mast cell activation syndrome and related disorders
- 40 Mast cell activation, unspecified
- 41 Monoclonal mast cell activation syndrome
- 42 Idiopathic mast cell activation syndrome
- 43 Secondary mast cell activation
- 49 Other mast cell activation disorder

Table 2. Conditions suspected of involving activation of mast cells.

- Alpha-Hypertyptasemia
- Amyotrophic lateral sclerosis (ALS)
- Alzheimer's disease (AD)
- Attention deficit/hyperactivity disorder (ADHD)
- Autism spectrum disorder (ASD)
- Chronic inflammatory response syndrome (CIRS)
- Coronary hypersensitivity (Kounis) syndrome
- Dysautonomia syndrome
- Endometriosis
- Eosinophilic esophagitis/gastroenteritis
- Familial hyper IgE syndrome
- Interstitial cystitis/Painful bladder syndrome (IC/PBS)
- Irritable bowel syndrome (IBS)
- Long-COVID syndrome
- Macrophage activation syndrome
- Migraine headaches
- Multiple chemical sensitivity syndrome
- Multiple sclerosis
- Multisystem inflammatory syndrome (MIS)
- Myalgic encephalomyelitis/Chronic fatigue syndrome (ME/CFS)
- Neurofibromatosis
- Pediatric acute neuropsychiatric syndrome (PAN)
- Periodontal disease
- Post-Lyme syndrome (PLS)
- Psoriasis
- Sick building syndrome (SBS)
- Toxic mold syndrome (TMS)
- Traumatic brain injury (TBI)
- Vitiligo

Table 3. Diseases confused with mast cells disorders.

- Angioneurotic edema
- Carcinoid syndrome
- Cryopyrin diseases
- Dysautonomia
- Scleroderma
- Scombroid (histamine) toxicity
- Vasovagal attack

Table 4. Laboratory tests for diagnosis of atopic conditions.

Blood
- IgE, IgG_1, IgG_4
- Immune IgE (RAST for alpha-gal, casein, gluten, dust mites, fungi, grass, pollen)
- Anti-IgE receptor antibody (basophil activation test)
- CCL2, CXCL8 (IL-8)
- Food Intolerance Panel (immune $IgG_{4)}$
- IL-4, IL-6, IL-31
- Tryptase

Urine 24 hours or first-morning void (must be kept and sent cold)
- LTE_4
- N-Methylhistamine (NMH) or methylimidazole acetic acid (MIA)
- PGD_2
- 2,3-Dinor-11b-PGF_{2a}

Table 5. Proposed characteristics for a subgroup of MCAS resistant to treatment.

- Presence of neurologic and cognitive symptoms
- Extreme sensitivity to odors and stress
- Variable elevated serum levels of:
- Chymase
- CRH
- Eosinophilic cationic protein (ECP)
- Heparin
- IL-6
- IL-31
- IL-33
- Matrix Metalloproteinase-9 (MMP-9)
- MRGPRX2
- Neurotrophins
- Osteopontin
- PAF
- SP

frequently elevated than N-methyl histamine or serum tryptase [92,93], but also the presence of neuropsychiatric symptoms. It was recently reported that patients with hereditary a-hyperpotassemia, unlike those with indolent systemic mastocytosis, did not have urine elevations of either N-methyl histamine or 2,3-dinor-11β-$PGF_2\alpha$ [94]. A recent review tried to associate some 'non-tryptase urinary and hematologic biomarkers' with MCAS symptoms [95].

The critical issue is not how to define certain syndromes, but how to define mast cell 'activation.' For instance, many patients with MCADs (e.g. allergies, asthma, cancer, urticarias) do not have elevated serum levels of tryptase [96]. This should not be surprising given the fact that mast cells can be stimulated by many neuroimmune- endocrine triggers [97], leading to the release of mediators other than histamine or tryptase [96].

Moreover, a subgroup of MCAS patients have extreme sensitivity to odors and stress, present with neurologic and cognitive dysfunction, and are resistant to treatment with antihistamines and/or leukotriene antagonists (Table 5). Such patients should be

investigated for additional mast cell-associated biomarkers such as IL-6, Osteopontin and vascular endothelial growth factor (VEGF) (Table 4) [98]. A somewhat analogous situation is that of Chronic Spontaneous Urticaria (CSU), in which about 40% of patients are resistant to treatment with antihistamines, but was characterized by elevated blood levels of the mast cell mediator platelet-activating factor (PAF) [99], which is also involved in inflammation [100]. In fact, elevated levels of PAF had been reported to better reflect the severity of anaphylaxis than either histamine or tryptase [101].

Many MCAS patients describe sudden mast cell reactivity to multiple triggers (old and new) following a major stressful event such as a death in the family, major surgery or extensive trauma. This hinged reactivity may be mediated via the action of corticotropin-releasing hormone (CRH) secreted under stress that has been repeatedly shown to worsen atopic conditions [102] and MCDAs. The main receptor for CRH [receptor-1 (CRHR-1)] was shown to be expressed in mast cells of two patients with mastocytosis [103], and functional on human mast cells leading to the selective release of VEGF without tryptase [104]. Hence, addressing stress should be considered in the treatment of MCADs.

3. Pathophysiology of mast cells

In addition to FceRI, mast cells express multiple surface receptors for a variety of stimuli (Table 6) [97,105], including receptors for sex hormones [106]. Mast cells also can synthesize hormones [107] and neuropeptides such as CRH [108], as well as the peptides hemokinin-1 (HK-1) [109], NGF [110], neurotensin (NT), substance P (SP) [111] and other neurotrophins [112]. Mast cells in the pineal and the hypothalamus may also be involved in circadian rhythms [113–115]. There are also a number of putative inhibitory receptors (Table 7) [116], such as CD300a [117–120], as well as Siglet-6 [121], Siglec-7 [122,123] and Siglec-8 for which an anti-Siglec-8-antibody was recently reported in a Phase II study to improve antihistamine-resistant CSU [124].

The mode and extent of mast cell responsiveness ultimately depend on the interplay between stimulatory and inhibitory signaling pathways (Tables 6 and 7) [125].

Mast cells are also triggered by non-IgE stimuli [19,126,127] and by additional ligands [128], including complement fragments [129,130] neuropeptides [97], such as CRH [131], HK-1 [109], NGF [110], NT [132], SP [133] and somatostatin [134,135] via high-affinity receptors, as well as by many cationic compounds through the low-affinity G-coupled receptor MRGPRX2 [136]. This latter process is distinct from that utilizing the FceRI and may lead to the release of different mediators. Responses due to degranulation of mast cells via activation of MRGPRX2 and FceRI were reported to be additive [137]. Moreover, the alarmin IL-33 was shown to amplify production of pro-inflammatory cytokines via activation of either MRGPRX2 or FceRI [138]. Mast cells can also be stimulated via activation of toll-like receptors (TLRs) [139,140] pathogens, toxins [141], and pathogens [142–144] as well as viruses [145,146] including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [147–153]. Mast cells also communicate with T-cells during immune response [154,155]. In fact, mast cells can function as antigen-presenting cells [156] and induce the maturation of dendritic cells [157].

Table 6. Main mast cell stimulatory receptors.

Receptor	Ligand/Stimulus
A2A, A2B, A3	Adenosine
Ach-m	Acetylcholine
ACTH-R	Adrenocorticotrophin
ACE2	Angiotensin 2
Beta2-Adrenoreceptor	Adrenaline
Cannabinoid CB2 receptor	2-arachidonoyl-glycerol, anandamide
C3a, C5a	Complement
CD3, CD25,CD34,CD66,CD326	Unknown
CXCR1–4	Chemokines
CD47	Integrins
CD48	2B4
CD117 (KIT)	Stem cell factor
CD226/DNAM-1	Nectin-2 (CD112)
CD300	Eosinophilic Cationic proteins
CLR (calcitonin receptor-like receptor)	Calcitoningene related peptide)
CRHR-1, 2	CRH, urocortin
EMR2	Vibrations
Estrogen receptors A,B	Estrogens
ETA, B	Endothelin-1
FcalphaR (CD89)	IgA
FcepsilonR	IgE
FcgammaRI, RIIA, RIIB, RIII	IgG
GABA-A, B, C	Benzodiazepines, gamma-aminobutyric
NMDAR, AMPAR, and kainate receptors	Gluatamate
Heparan sulfate	Bacterial, viral antigens
H1, H2, H3, H4	Histamine
IL-1R1	IL-1beta
IL-4 R	IL-4, IL-13
IL-6 R+IL6ST/GP130/IL6-beta	IL-6
IL-10R1,2	IL-10
IL-17 R	IL-17
IL-18Ralpha+IL-18Rbeta	IL-18
IL-36 R	IL-38
LDL, VLDL	Apolipoprotein E
Mel1a, Mel1b, MT1, MT2	Melatonin
NGFR (CD271 or p75 neurotrophinR)	Nerve growth, brain-derived neurotrophic factor
MHCI, II	Antigenic peptides and drugs
MRGPRX2	Cationic peptides
NK-1	Substance P, hemokinin-1
NT3	Neurotensin
Opioid receptors	Endorphins, enkephalins
PAF-R	Platelet-activating factor
Protease-activated receptor-2 (PAR-2)	Proteases
Progesterone receptor	Progestins
PTHR1 (PTH/PTHrP type 1 receptor)	Parathyroid hormone
Purinoreceptors	ATP
STTR1-STTR5	Somatostatin
ST2	IL-33
TGFBR1,2 and 3	TGFbeta
TLR(1–9)	DAMPs, Pathogens
VDR	Vitamin D

Upon stimulation, mast cells rapidly secrete via degranulation multiple mediators [158] that include preformed, granule-stored mediators such as heparin, histamine, tryptase and tumor necrosis factor (TNF) [3]. Histamine has been the main mediator associated with mast cells [159] but is also released from basophils [160]. Interestingly, mast cells can also generate a histamine-releasing peptide from albumin [161], meaning that once stimulated mast cells can release enzymes that can act on albumin and produce a peptide that can further stimulate mast cells. The serine proteases chymase and tryptase are considered to be stored in the same secretory granules. Tryptase has been studied extensively because it is considered an exclusive mast cell-

Table 7. Main mast cell inhibitory receptors.

Receptor	Ligand
Allergin-1	Inhibitory
ALX/FPR2	LXA_4 (proresolving)
CD200R	CD200 glycoprotein
Glyceraldehyde-3-phosphate dehydrogenase (GAPDH)	Lactoferrin
IL-10RI and IL-10RII	IL-10
IL-18Ra and IL-1R8	IL-37
IL-36 R a	IL-38
Nucleotide converting ectoenzymes (E-NDP1,3,7)	ATP
Peroxisome proliferator-activated receptor gamma (PPAR-γ)	15d-prostaglandin J2 (15d PGJ_2)
Protein tyrosine phosphatase (PTPs)	Chondroitin sulfate
IRp60	Unknown
Siglec-6,7,8	Unknown
Thrombomodulin	Thrombomodulin (soluble)
TMEM184A	Heparin

associated mediator and is released during anaphylaxis and systemic mastocytosis [162,163], as well as in many cases of MCAS [164]. Tryptase activates the pro-inflammatory protease-activated receptors (PARs) and generate anaphylatoxins (C3a, C5a) [165]. However, there are a number of unexplained findings related to tryptase [166]: (a) Elevated PAF levels are better correlated with anaphylaxis than tryptase or histamine [101]; (b) lack of tryptase elevations in many patients with MCAS [96]; (c) acute increases in serum tryptase were not associated with symptoms in diffuse cutaneous mastocytosis [167]; and (e) mast cell activation in patients with coronavirus disease 2019 (COVID-19) was associated with serum greater elevations of chymase, than tryptase or other mast cell mediators [151]. This latter finding may be possibly due to the preferential activation of pulmonary mucosal mast cells that contain chymase but not tryptase.

Mast cells also secrete newly synthesized mediators 6–24 hours after stimulation (late- [151] phase reaction); these include prostaglandin D_2 (PGD_2) [168], cytokines (IL-5, IL-6, IL-31, IL-33 and TNF-α) and chemokines (CCL2, CCL5 and CXCL8) [4,5,169], as well as PAF [170,171] which has been implicated in micro thromboses [172,173] and inflammation [172]. PAF is the most potent trigger of platelet aggregation known, but it is extremely short-lived making its routine measurement difficult [174]. PAF is involved in allergies [175] such as allergic rhinitis [176–178] immediate and late cutaneous reactions [179], as well as chronic spontaneous urticaria (CSU) [99]. Combination treatment blocking both PAF and histamine by the histamine-1 receptor antagonist rupatadine markedly reduced the severity of peanut-induced anaphylaxis [180]. PAF also stimulates mast cells [170] and eosinophils [181,182], as well as induces IL-6 production [183–185], which in turn stimulates the production of PAF [186,187]. Mast cells also secrete mitochondrial DNA that induces autocrine and paracrine inflammatory responses [188].

4. Selective release of mediators

Mast cells can release specific mediators via differential release mechanisms [189]. It was first shown that was possible for serotonin [190–192], and VEGF [49] without degranulation, but rather via intragranular changes associated with the release of mediators without the release of histamine or tryptase [193]. It had been also reported that mast cells can release the content of individual secretory granules [194] or individual mediators without degranulation [190]. This process was distinct from 'piece-meal degranulation' that had already been reported [195], granule-associated vesicle transport [196], or the release of extracellular vesicles [197–203].

Mast cells could also form antibody-dependent 'synapses' for dedicated secretion [203,204] and also communicate via the formation of nanotubes [205]. The 'alarmin' IL-33 [96,206,207] stimulates mast cells via activation of their own specific surface receptor, ST2/IL-33, significantly increasing the ability of SP to stimulate the release of VEGF [133,208], IL-31 [209], TNF [210] and IL-1β [211] as well as CCL2 and CCXL8 [212] and other newly synthesized mediators [96]. It was recently reported that VEGF and other angiogenic factors were elevated in the serum of patients with mastocytosis and the degree of elevation correlated with disease severity [213,214]. VEGF is also vasodilatory and was shown to be increased in lesional skin in CSU [213].

IL-33 also augments the release of IL-31 from human mast cells stimulated either by SP or IgE/anti-IgE [112]. Mast cells can release IL-33, themselves [116]. Mast cell-derived IL-1β or histamine-induced release of IL-1β from macrophages [215] can then stimulate mast cells to release IL-6 selectively without degranulation [191,192]. IL-6 is elevated in MCADs and correlated with disease severity [216–218] and is also elevated in COVID-19 [122;123]. In fact, IL-6 promotes an increase in mast cell numbers [219], and is constitutively released in the presence of the D816V-KIT mutation [220]. The mode and extent of mast cell responsiveness ultimately depend on the interplay between stimulatory and inhibitory signaling pathways (Tables 6 and 7).

Secretion of mediators can occur utilizing different signaling [20,221–223] and secretory [221,223] pathways (Figure 1).

5. Epigenetic regulation of mast cell functions and mast cell-associated disorders

Epigenetics refers influence of environmental and behavioral events that alter genes without changing the DNA sequence via DNA methylation, posttranscriptional modifications through non-coding RNAs, histone modifications and nucleosome positioning that affects DNA and chromatin structure [224].

Epigenetic modifications can be suppressed, cured and reversible including in MCAD [225]. Mast cells could undergo epigenetic programming that maintains a stable identity but can undergo significant plasticity to adjust to different environmental challenges [226]. Though the implication of epigenetic changes in the pathogenesis of systemic mastocytosis is not yet clearly known [224], several reports indicated epigenetic modifications may be involved in MCADs [225,227,228]. In fact, epigenetic mechanisms could contribute to the familial type of systemic MCAD [228]. In particular, some mast cell mediators could have autocrine effects. For example, tryptase could catalyze histone clipping as a novel epigenetic mechanism in mast cells [229], and tryptase could regulate the epigenetic modification of histones in mast cell leukemia cells [230].

DNA methyltransferase 3A (DNMT3A) and DNA methylation play a significant role in acute and chronic mast cell activation conditions [231]. Mastocytosis could be treated with inhibitors of histone methyl transferase that can cause cell death by apoptosis [232]. Epigenetic changes in macrocytosis may include mutations in the genes such as TET1, DNA methyltransferase enzyme DNMT3A, ASXL1 and gene methylation in neoplastic cells [224]. Ten-eleven translocation-2 (TET2) is an epigenetic regulator and its expression is induced in response to both acute and chronic activation of mast cells [226,233]. A recent study showed that butyrate, a histone deacetylase (HDACs) suppresses the activation of human mast cells through the epigenetic regulation of the FcεRI-mediated pathway [234]. Phosphorylation of a 78kD protein or serine and threonine residues [235], which was later shown to be moesin [236], was shown to be associated with inhibition of secretion in rat mast cells [237] and basophils [238]. Primary mast cells from systemic mastocytosis patients are highly sensitive to suberoylanilide hydroxamic acid (SAHA)-induced cell death, whereas normal bone marrow mast cells are resistant. Thus, HDAC inhibitors may be a potential clinical treatment option for SM patients [239]. Histone acetylation is implicated in immune response associated with mast cell activation. Moreover, dietary substances could alter mast cell functions through epigenetic mechanisms [240]. An *in vitro* study demonstrated the role of epigenetics in the expression of CD34 and transcription factor HIF1A during the differentiation process of mast cells [241]. These reports indicate that epigenetic mechanisms could influence mast cell function and contribute to mast cell disorders.

6. Effect of neuropeptides

Most patients with MCADs present with neuropsychiatric symptoms and cognitive dysfunction [242–244]. The regulation of mast cells by neurotransmitters and neuropeptides has been reviewed [97,245,246], with emphasis on CRH [131], HK-1 [109], NGF [110], NT [132], SP [133] and somatostatin [134,135] acting via activation of high-affinity receptors.

Mast cells are also present in the central nervous system (CNS) [247,248], especially in the meninges [249,250], and the median eminence [249,251,252] where they are located perivascularly close to neurons [253] that are often positive for CRH secreted under stress [249]. Mast cells are the richest source of histamine in the CNS [254], particularly in the amygdala, hippocampus, hypothalamus and thalamus [255–257]. Brain mast cells had been termed the 'immune gate to the brain' [247]. Histamine is involved in neuronal development [258], and also acts as an alert signal in the brain [259]. In fact, brain histamine is critical for arousal [260,261], memory consolidation [262] and retrieval [263–265], as well as motivation [255]. Activated brain mast cells were shown to contribute to postoperative cognitive dysfunction via activation of microglia [266] involving mediators [267]. Cognitive dysfunction is common in mastocytosis patients [268,269] and may be related to morphological brain abnormalities, Primarily punctuated white matter abnormalities, that may potentially explain 'brain fog.'

The effect of stress on mast cells has also been reviewed [102,270]. Restraint stress in rodents increased blood-brain barrier (BBB) permeability [251,271,272] via CRH-stimulating mast cells [271,273,274]. Mast cell-derived mediators, such as cytokines [275,276], increased BBB permeability not only to small molecules [251,271] but also to mammary adenocarcinoma brain metastases in mice [273]. This process could worsen with stress acting via CRH stimulation of mast cells [271,273], leading to increased dura vascular permeability, an effect that was absent in mast cell-deficient mice [277]. Interestingly, meningeal mast cells affected the integrity of the BBB and promoted T-cell brain infiltration [278].

Allergic stimulation of nasal mast cells resulted in stimulation of the hypothalamic-pituitary-adrenal (HPA) axis [131,279–281], possibly via mast cell release of histamine [282], IL-6 and CRH [108].

Mast cell responsiveness may be regulated not only by the neuroimmune stimuli but also by the effects of the different receptors involved. For instance, mast cells express high-affinity neurokinin-1 (NK-1) receptors for SP [210,283,284]. Moreover, SP [284] and NT [285] -induced the expression of CRHR-1 in human mast cells. Secretion of mediators can occur utilizing different signaling [20,221–223] and secretory [221,223] pathways. Interestingly, a circadian clock was reported to regulate IgE-dependent activation of murine bone marrow-derived mast cells [114,286,287].

7. Treatment approaches of mast cell-mediator-induced disorders

There are still no clinically effective inhibitors of mast cell activation ('mast cell stabilizers') [16,23,288,289]. Biologics have been used [17,290], mostly aiming at neutralizing the effect of IgE in urticaria with the use of omalizumab [291,292]. A number of inhibitors of tyrosine kinase (KIT) have been developed to block mast cell proliferation [293–295], but most of these drugs do not inhibit mast cell activation [296,297]. New approaches target the putative inhibitory receptor (Siglec-8) [17,298,299]. Disodium cromoglycate (cromolyn) is known as a 'mast cell stabilizer' because it had originally been shown to inhibit histamine release from rat peritoneal mast cells [237]. However, cromolyn does not effectively inhibit either mouse [300] or human [301] mast cells.

Minimizing exposure to potential triggers (e.g. allergens, foods, heat, stress) is clearly important. If there allergy to food antigens [302,303] or histamine intolerance is present [304], supplementation with the main histamine metabolizing enzyme, diamine oxidase (DAO) [305] shortly before meals could be beneficial especially if its activity is low or there is the presence of gene polymorphisms. The initial treatment approach is the use of second-generation, H-1 antihistamines up to 4 times the recommended doses as tolerated [306–310]. Unique among these, is the histamine-1 receptor antagonist rupatadine, which was specifically developed to have potent anti-PAF activity [311]. Rupatadine is not available in the US although it has been available in Europe for over 20 years and in Canada since about 2000 (Canadian online pharmacies will send it with a US prescription). Rupatadine at 40 mg/day is well tolerated and inhibits histamine- and PAF-induced flares and *ex vivo* platelet aggregation in normal male subjects [312]. When compared to other

second second-generation H-1 antihistamines in chronic urticaria, 20 mg/day of rupatadine showed the greatest efficacy in the treatment of CSU (71.6%) as compared to 20 mg/day of desloratadine (50%), and 20 mg/day of levocetirizine (21.7%) Notably, rupatadine also inhibited histamine and TNF release from human mast cells in response to PAF [256], and the release of histamine and IL-6 from human mast cells was stimulated by different triggers [313]. Rupatadine, unlike desloratadine and levocetirizine, also inhibited the PAF-induced release of histamine from human mast cells [314].

The first-generation H1 anti-histamine-1 ketotifen has been promoted as a mast cell inhibitor, but the evidence is weak [315,316] and it is associated with fatigue and weight gain.

Addition of H2- antihistamines may have additional benefits as cimetidine [317], ranitidine [318], and famotidine [319] have been reported to also inhibit rat mast cells. Interestingly human leukemic (HMC-1) and human skin mast cells primarily express H2 receptors [320].

Increasing evidence supports the premise that Vitamin D has immunoregulatory actions in general [321]] and mast cell inhibitory functions in particular [322]. Specifically, vitamin D was reported to regulate IgE production [323] and inhibit IgE-dependent mast cell activation via specific vitamin D metabolites [324] and also inhibit ultraviolet B (UVB) irradiated skin mast cells [325]. Even though the precise mechanism is not known, the beneficial action of vitamin D may involve increased expression of the vitamin D receptor (VDR) receptor and inhibition of Lyn binding to FceRI [326]. Vitamin D may also be important in inhibiting IL-33-associated mast cell activation as it was shown to enhance the production of soluble ST2 (IL-33sr), thus inhibiting the availability and action of IL-33 [327].

Certain naturally occurring flavonoids, commonly found in fruits, green plants and seeds, have potent antioxidant and anti-inflammatory properties [328,329]. Among these, the flavone luteolin stands out because it significantly inhibits the activation of both mast cells [301,330] and the brain macrophages, and microglia [331–334]. The novel luteolin structural analogue tetramethoxyluteolin (methoxyluteolin) is an even more potent inhibitor than luteolin [210,301,330,334] and has been incorporated into a skin lotion. Flavonoids have also been reported to modulate the synthesis of PAF [335], which has been strongly implicated in COVID-19 [336]. Luteolin especially formulated in olive pomace oil [337] to increase absorption may not only inhibit mast cell activation but also prevent neuroinflammation [338–341], is neuroprotective [338,342–344] and could reduce cognitive dysfunction [345–349], especially brain fog [350–352], the main complaint of many patients with MCADs [269,353]. However, data from controlled clinical trials are still lacking.

8. Conclusions

Mast cells play a critical role in atopic diseases [39], especially allergies [19] and anaphylactic reactions [2,39,354], but also in inflammation [2;44;202;204;205]. Symptoms associated with mast cell activation are numerous and can affect all organs making the presentation of patients confusing and diagnosis challenging. Symptoms may derive from numerous mediators released from mast cells other than histamine and tryptase necessitating a better definition of mast cell activation. Early diagnosis and appropriate intervention, along with stress reduction, could minimize mast cell reactivity and improve quality of life.

9. Expert opinion

Great advances have been made in the potential treatment of the MCAD variant aggressive systemic mastocytosis.

There have been few advances in the development of better diagnostic panels for mast cell activation. Potential useful new serum biomarkers that would need to be validated could include CRH, eosinophil cationic protein (ECP), IL-6, MMP-9, neurotrophins, osteopontin [355,356], PAF, SP [357], as well as VEGF and other angiogenic factors [208,213,214,355,356,358]. Elevated serum levels of the nonspecific mast cell surface receptor MRGPRX2 may also be useful [359].

The ultimate goal should be better diagnosis and treatment of mast cell activation, especially in response to non-allergic triggers.

There should be directed funding toward better phenotyping of mast cells, especially in different conditions, developing useful biomarker panels for diagnosis of MCAS understanding the mechanism of selective mediator release without degranulation, and identifying ways to regulate mast cell reactivity and activation.

Critical for advancing the field is the availability of cultured primary human mast cells since the closest source so far is still immortalized leukemic mast cells [360] and since bone marrow-derived mast cells do not necessarily reflect the tissue mast cell phenotype [361].

Human organoids [362] with mast cells and other tissue cells (e.g. endothelial cells, fibroblasts, T cells, and brain cells) should be developed to mimic specific tissue environments and mast cell phenotype differentiation.

Brain mast cells should be studied as they may be involved in neurodevelopmental and neuroinflammatory conditions [76,245,363], especially since brain mast cells may not express FceRI [364] but are able to release TNF [278] in response to other triggers.

Better research and education on aspects of mast cell activation-related diseases and their treatment, as well as increased communication among health professionals, is important in order to diagnose and treat MCADs [365].

Abbreviations

11β-$PGF_2α$	11β-Prostaglandin F2α
BBB	Blood-brain barrier
CCL2	C-C motif chemokine ligand 2
RANTES	Regulated on Activation, Normal T Expressed and SecretedCD117
	Cluster of differentiation 117
CNS	Central nervous system
COVID-19	Coronavirus disease of 2019
CPA3	Carboxypeptidase A3
CRH	Corticotropin-releasing hormone
CRHR-1	Corticotropin-releasing hormone receptor 1
CSU	Chronic spontaneous urticaria
CTMC	Connective tissue mast cells
CXCL8	C-X-C motif ligand 8
ECP	Eosinophil cationic protein

EDS	Ehlers Danlos syndrome
EMR2	=EGF-like module-containing mucin-like hormone receptor-like2
FcεRI	Fc epsilon receptor 1
HK-1	Hemokinin-1
HPA	Hypothalamic-pituitary-adrenal axis
IgE	Immunoglobulin E
IL-1beta	Interleukin 1β
IBS	Irritable bowel syndrome
MCADs	Mast cell activation diseases
MCAS	Mast cell activation syndrome
MCAU	Mast cell activation unspecified
MCP-1	Monocyte chemoattractant protein 1
MCSS	Multiple chemical sensitivity syndrome
MMAS	Monoclonal Mast cell activation disorder
MMC	Mucosal mast cell
MMP	Matrix metalloproteinases
MMP-9	Matrix metalloproteinase-9
MRGPRX2	MAS-related G protein-coupled receptor-X2
NGF	Nerve growth factor
NK1	Neurokinin-1
NT	Neurotensin
PAF	Platelet-activating factor
PGD2	Prostaglandin D2
POTS	Postural orthostatic tachycardia syndrome
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SCF	Stem cell factor
Siglec-8	Sialic acid-binding immunoglobulin-like lectin 8
SP	Substance P
TNF	Tumor necrosis factor
VEGF	Vascular endothelial growth Factor

Declaration of interest

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