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MAST CELLS IN ATOPIC DISEASES: MORE THAN JUST HISTAMINE

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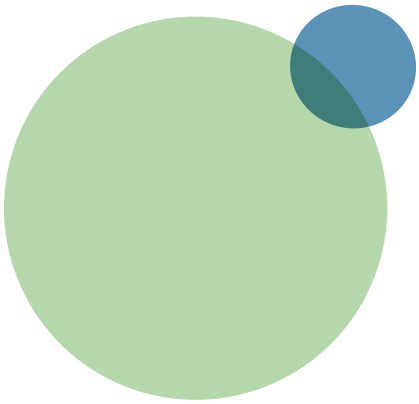

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MAST CELLS IN ATOPIC DISEASES: MORE THAN JUST HISTAMINE

Abstract

Mast cells are present in all tissues and are able to release multiple mediators in response to allergic, autoimmune, environmental, neurohormonal and pathogenic triggers. Histamine has received most of the attention in terms of pathophysiology and drug development, while tryptase remains to this date with no clear function and no known inhibitor. Mast cells can also release pro-inflammatory and pruritogenic molecules, such as IL-6 and IL-31, selectively without degranulation. One such critical molecule is platelet activating factor (PAF), which is vasoactive, can cause wheal and flare on its own, but can also stimulate eosinophils and mast cells that are critical in the pathogenesis of chronic spontaneous urticaria (CSU) and rhinitis. Mast cell-derived cytokines and PAF have also been implicated in inflammatory processes including COVID-19. Among the second generation histamine-1 receptor antagonists, rupatadine is more effective overall, it has potent anti-PAF activity, and also inhibits activation of human mast cells and eosinophils. Rupatadine could, therefore, serve as a first-line drug for CSU and rhinitis, but may also be used, especially for patients resistant to antihistamines.

Biology of Mast Cells

Mast cells[1-5] derive from hematopoietic precursors,[6] travel in the circulation as precursor cells and proliferate in response to stem cell factor (SCF), the ligand of the surface tyrosine kinase receptor CD117 (C-KIT).[7] Mast cells mature and are located perivascularly[8-10] in all tissues[11] under the influence of local micro-environmental factors[12, 40] resulting in different phenotypes.[13] Mast cells are present in the brain,[14,15] including the meninges,[16,17] and the median eminence[16,18,19] where they are located perivascularly in close proximity to neurons[20] that are positive for corticotropin releasing hormone (CRH).[16] Brain mast cells are the richest source of histamine,[21] which is involved in neurodevelopment.[22] Furthermore, histamine may serve as an alert signal in the brain when high attention or a strong wake-drive is needed, such as during exploration, learning and motivation.[23] Brain mast cells have been associated with memory consolidation and retrieval,[24-26] as well as arousal[27,28] and motivation.[29,30]

Mast cells are typically activated by allergens crosslinking specific immunoglobulin E (IgE) bound to high affinity surface Fc epsilon receptor 1 (FcεRI).[31,32] Even though mature mast cells reside in the tissues, they probe the blood vessel lumen by extending filopodia through endothelial gaps, capturing IgE from the circulation, and sensing circulating antigens.[33] Contrary to early research, fetal mast cells can bind maternal circulating IgE and contribute to postnatal allergic responses.[34] Quite surprisingly, prenatal stressful events have been reported to increase cord blood IgE.[35]

Mast cells are also triggered by non-IgE stimuli[36-38] and by additional ligands,[39] including neuropeptides,[40] such as CRH,[41] neurotensin (NT),[42] substance P (SP)[43] and somatostatin[44,45] via high affinity receptors (**Table 1**), as well as by many cationic compounds through the low affinity G-coupled receptor MRGPRX2.[46] This process is distinct from that utilizing the FcεRI and may lead to release of different mediators. Allergic stimulation of mast cells leads to secretion of the SP-related peptide Hemokinin-1, which augments IgE-mediated allergic responses by binding with low affinity to the SP receptor (NK1) on mast cells.[47] CRH augmented release from human mast cells stimulated by IgE/anti-IgE of vascular endothelial growth factor (VEGF), which is also vasodilatory, could contribute to edema and has been shown to be increased in lesional skin in CSU.[48] Mast cells are also triggered by pathogens including fungi,[49] toxins,[50] as well as viruses[51,52] including SARS-CoV-2.[53,54] Mast cells express multiple receptors for a variety of stimuli (**Table 1**),[40,55] including receptors for sex hormones.[56] In addition, mast cells can synthesize hormones[57] and neuropeptides such as CRH,[58] as well as the

Table 1. Main Mast Cell Receptors	
Receptor	**Ligand**
A2A, A2B, A3	Adenosine
ACTH-R	Adrenocorticotrophin
ACE2	Angiotensin 2
Beta2-Adrenoreceptor	Adrenaline
Cannabinoid CB2 receptor	2-arachidonoyl-glycerol, anandamide
C3a, C5a	Complement
C-kit (CD117)	Stem cell factor
CXCR1-4	Chemokines
CD47	Integrins
CD300	Eosinophilic Cationic proteins
CRHR-1, 2	CRH, urocortin
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	Histamine
IL-1R1	IL-1beta
IL-4R	IL-4, IL-13
IL-6R+IL6ST/GP130/IL6-beta	IL-6
IL-10R1,2	IL-10
IL-17R	IL-17
IL-18Ralpha+IL-18Rbeta	IL-18
LDL, VLDL	Apolipoprotein E
Mel1a, Mel1b, MT1, MT2	Melatonin
NGFR (CD271 or p75 neurotrophinR) neurotrophic factor	Nerve growth factor, brain-derived
MHCI, II	Antigenic peptides
MRGPRX2	Cationic peptides
NK-1	Substance P, emokinin-1
NT3	Neurotensin
Opioid receptors	Endorphins, encephalins
PAF-R	Platelet activating factor
PAR	Proteases
Progesterone receptor	Progestins
ST2	IL-33
TGFBR1,2 and 3	TGFbeta
TLR(1-9)	DAMPs, Pathogens
VDR	Vitamin D

peptide neurotensin (NT),[59] which can sensitize sensory nerve endings and mediate the effect of stress. Mast cells in the pineal and the hypothalamus may also be involved in circadian rhythms.[60-63]

Upon stimulation, mast cells rapidly secrete via degranulation multiple mediators that include the preformed, granule-stored such as heparin, histamine, tryptase and TNF.[3] Histamine has been the main mediator associated with mast cells,[64,65] but is also released from basophils.[66] Interestingly, mast cells can also generate a histamine-releasing peptide from albumin,[67] meaning that once stimulated mast cells can release enzymes that can act on albumin and produce a peptide that can further stimulate mast cells. Mast cells also secrete newly synthesized mediators 6-24 hours after stimulation (late-phase reaction); these include prostaglandin D_2 (PGD_2),[68] cytokines (IL-5, IL-6, IL-31, IL-33 and TNF) and chemokines (CCL2, CCL5 and CXCL8), [4,5,69] as well as platelet activating factor (PAF),[70] which has been implicated in inflammation[71] and microthromboses.[71,72] PAF has many potent biological effects on almost all tissues and organs, leading to inflammation and microthromboses.[71] PAF is the most potent trigger of platelet aggregation known. It was discovered in 1972.[73] Its structure was elucidated in 1979 by Demopoulos and colleagues as a glyceryl-ether lipid (1-O-alkyl-2-acetyl-*sn*-glycero-3-phosphocholine).[74] PAF is produced by many prokaryotic and eukaryotic cells, but it is extremely short-lived making its routine measurement in biologic fluids difficult.[75]

Selective release of mediators

Mast cells can release *specific* mediators, such as serotonin,[76] IL-6[77] and VEGF[78] without degranulation, but rather via intragranular changes associated with release of mediators without release of histamine or tryptase.[79] In addition, the "alarmin" IL-33[80-82] stimulates mast cells via activation of its own specific surface receptor, ST2, significantly increasing the ability of SP to stimulate release of VEGF,[43,83] IL-31,[84] TNF[85] and IL-1β,[86] as well as CCL2 and CCXL8[87] and other newly synthesized mediators.[82] IL-33 also augments release of IL-31 from human mast cells stimulated either by SP or IgE/anti-IgE.[84] Mast cells can release IL-33, themselves.[88] Mast cell-derived IL-1β or histamine-induced release of IL-1β from macrophages[89] can then stimulate mast cells to release IL-6 selectively without degranulation.[77,90] IL-6 is elevated in systemic mastocytosis and correlated with disease severity,[91-93] and is also elevated in COVID-19.[94,95] In fact, IL-6 promotes an increase in mast cell numbers,[96] and is constitutively released in the presence of the D816V-KIT mutation.[97] IL-6 and other mast cell-derived molecules, such as bradykinin, IL-31, matrix metalloproteinase-9 (MMP-9) and PAF are quite pruritogenic (**Table 2**).

We had called brain mast cells the "immune gate to the brain"[14] and the "immunoendocrine master player."[98] Restraint stress in rodents increased blood-brain barrier (BBB) permeability[18,99,100] via CRH-stimulating mast cells.[99,101,102] Mast cell-derived mediators, such as cytokines,[103,104] increased BBB permeability not only to small molecules,[18,99] but also to mammary adenocarcinoma brain metastases in mice.[101] This process could worsen with stress, including psychological stress acting via CRH stimulation of mast cells[99,101] leading to increased dura vascular permeability[105]-- an effect that was absent in mast cell-deficient mice.[106] Allergic stimulation of nasal mast cells resulted in stimulation of the hypothalamic-pituitary-adrenal (HPA) axis,[41, 107-109] possibly via mast cell release of histamine,[110] IL-6[111] and CRH.[58] The regulation of mast cells by neuropeptide and neurotransmitters was reviewed recently.[40,112,113]

The mode and extent of mast cell responsiveness ultimately depends on the interplay between stimulatory and inhibitory signaling pathways. 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 NK-1 receptors for SP.[85,114] Moreover, SP[115] and NT[116] induced the expression of CRHR-1 in human mast cells. Secretion of mediators can occur utilizing different signaling[117-120] and secretory[117,121] pathways. The diagnosis of atopic diseases rests on clinical symptoms and the measurement of a number of molecules in the blood and urine (**Table 3**). However, there are no specific mast cell markers;[122] histamine is degraded within a few minutes, while tryptase reflects the mast cell volume rather than its activation. Moreover, mast cells are also implicated in both health and disease,[38,123,120,124] especially immunity[125,126] and inflammation.[38,127,128]

Pathophysiology of Chronic Spontaneous Urticaria (CSU)

CSU is a common skin condition characterized by wheals and flares, but also intense itching, with or without angioedema[129,130] and constitutes a major global health burden.[131]

Mast cells are a necessary component in the pathogenesis of CSU,[132] but so are eosinophils.[133]

CSU is a clinical diagnosis. In spite of proposals for potential blood biomarkers, to date there is no consensus of specific biomarkers for CSU.[134,135] Elevations of

D-Dimer, eosinophil cationic protein (ECP), IL-6, matrix metalloproteinase-9 (MMP-9), PAF, TNF and vitamin D3 are the most useful markers for the diagnosis of CSU (**Table 4**). In addition, the presence of dermatographia and a positive anti-FcεRI IgG (basophil activation test) are commonly present in such patients (**Table 4**). Elevated mean serum IgE levels and blood eosinophils, along with the presence of positive skin prick tests to aeroallergens, correlates with the presence of anti-FcεRI IgG and anti-IgE IgG.[136] It was recently shown that elevated serum levels of the non-specific mast cell surface receptor MMRGPRX2 correlated with disease severity in CSU.[137] These findings may explain why as many as 30% of patients with CSU are resistant to antihistamines (**Table 4**).[131,138]

Elevated PAF levels had been strongly associated with severe anaphylaxis,[139,140] more so than histamine or tryptase.[141] Moreover, combination treatment blocking both PAF and histamine markedly reduces the severity of peanut-induced anaphylaxis.[142] PAF is also reported to be involved in allergies in general,[143] and more specifically in allergic rhinitis,[144,145] immediate and late cutaneous reactions,[146] as well as CSU.[147]

With respect to allergic rhinitis,[145] PAF has been identified in nasal polyps and eosinophils,[144] and has been shown to stimulate eosinophils,[148,149] especially superoxide ion generation.[150] More specifically, PAF is believed to be more potent than histamine in increasing nasal airway resistance.[151] PAF appears to have a bidirectional association with cytokines. For instance, IL-6 stimulates production of PAF,[152,153] while PAF induces IL-6 production.[154-156] Elevated blood PAF levels have been reported in patients refractory to treatment with antihistamines.[147] Additionally, PAF-induced wheal and flare reactions on their own, are

Table 2. Pruritogenic Molecules Released From Mast Cells
• Adenosine
• Bradykinin
• LTC_4
• Histamine
• IL-6
• IL-31
• MMP-9
• PAF
• PGD_2
• Substance P (SP)
• TNF
• Tryptase

Table 3. 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
• Heparin
• IL-4, IL-6, IL-31
• PGD_2
• 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-11β-PGF_{2a}

independent from histamine.[157] These findings indicate that PAF plays a major role in CSU by having a direct effect on the skin independent of histamine, but also stimulating mast cells to release other pruritogenic molecules.

A key aspect of CSU is pruritus .[158, 159] As mentioned earlier, a number of mast cell-derived molecules are involved in pruritus (**Table 3**), especially IL-31,[160-162] which has been reported to be elevated in CSU.[163] Research has demonstrated that human mast cells can release IL-31 in response to allergic and non-allergic triggers, especially IL-33.[84] Unfortunately, IL-31 is not yet measured in clinical laboratories.

Pruritus in general,[164] and in CSU specifically,[165] worsens with stress. Pruritus is mediated by neuroimmune circuits,[166] especially the interactions between peripheral nerves, mast cells and eosinophils.[167] In this context, it may be relevant that PAF stimulates expression of histamine-1 receptors in trigeminal ganglia,[168] implying that it may have a similar action on cutaneous sensory nerves resulting in increased sensitivity to histamine.

Table 4. Patients Resistant to Antihistamines

1. Angioedema
2. Presence of Dermatographia
3. Anti-IgE IgG
4. Positive Anti-FcεRI IgG (basophil activation test)
5. Elevated serum levels of:
• D-Dimer (angioedema)
• Eosinophilic cationic protein (ECP)
• IgE
• IL-6
• IL-31
• Matrix Metalloproteinase-9 (MMP-9)
• MRGPRX2
• Platelet Activating Factor (PAF)
• TNF
6. Decreased Vitamin D3 (1,25-OH)

Role of mast cells and PAF in COVID-19

The pathogenesis of most patients with COVID-19 is significant for the presence of perivascular inflammation and microthrombi[169-171] that could involve PAF.[71,72,172] The mediators involved could be released from mast cells.[72,89,173-177] Mast cell degranulation associated with interstitial edema and immunothrombosis has been reported in the alveolar septa of deceased patients with COVID-19.[54] In fact, mast cell-derived chymase was shown to be elevated in the serum of patients with COVID-19[178,179] as have been eosinophil-related mediators.[179] Another study reported increased number of eosinophils in the blood of patients with COVID-19.[180] Interestingly, many COVID-19 patients also develop urticaria.[181,72, 89,173-177]

Many patients (30-50%) infected with SARS-CoV-2 develop a post-acute syndrome a few months after the initial infection[182-186] known as post-acute COVID or "long-COVID."[183,187-189] Long COVID is particularly associated with persistent fatigue[190] and cognitive dysfunction, known as brain fog.[183,188,189,191-197] Symptoms experienced by COVID patients, especially cognitive dysfunction,[198-200] are similar[174,175] to those present in patients with mast cell activation syndrome (MCAS).[201,202] Mast cells in such patients can be stimulated by environmental and stress triggers[11] and viruses[52] including SARS-CoV-2.[53,176,203]

Treatment approaches

There are still no clinically effective mast cell inhibitors.[204, 205] A number of inhibitors of the tyrosine kinase c-kit receptor that block mast cell proliferation have been developed,[206,207] but most of them do not inhibit mast cell activation.[208] Disodium cromoglycate (cromolyn), known as a "mast cell stabilizer," had originally been shown to inhibit rat peritoneal mast cell histamine release.[209] However, cromolyn does not effectively inhibit either murine mast cells[210] or human mast cells.[212-214] The first generation histamine-1 receptor antagonist ketotifen has been promoted as a mast cell inhibitor, but the only such evidence is from a few studies using conjuctival mast cells, and it is very sedating. New approaches address new histamine receptors,[211] such as the putative inhibitory receptor (Siglec-8).[138,212,213]

Avoidance of potential triggers (**Table 5**) is self-evident. Supplementation with the main histamine metabolizing enzyme, diamine oxidase[214] and Vitamin D3,[215] which has been shown to modulate immune responses[216] and suppresses the production of VEGF from mast cells in CSU[217] may be helpful.

The initial treatment approach is the use of second-generation, non-sedating histamine-1 receptor antagonists up to 4 times the recommended doses as tolerated (**Table 5**).[129,218-221] One of these, the histamine-1 receptor antagonist rupatadine, was specifically developed to have potent anti-PAF activity.[222] The relative potency of rupatadine for blocking the histamine-1 receptor using histamine-induced guinea pig ileum contraction was shown to be about 24x greater than cetirizine and 75x greater than loratadine.[223] Rupatadine at 40 mg/day is well tolerated and inhibits histamine- and PAF-induced flares and *ex vivo* platelet aggregation in normal male subjects.[224] When compared to other non-sedating antihistamines in chronic urticaria, 20 mg/day of rupatadine showed the greatest efficacy in the treatment of CSU (71.6%) as compared to 80 mg/day of bilastine (60%), 20 mg/day of desloratadine (50%), 240 mg b.i.d. of fexofenadine (56%), and 20 mg/day of levocetirizine (21.7%).[225] In a network meta-analysis comparing the efficacy of second-generation antihistamines in CSU, rupatadine was superior to other antihistamines including bilastine with respect to change from baseline in pruritus and wheal scores.[226]

Notably, rupatadine also inhibited histamine and TNF release from human mast cells in response to PAF,[36] and the release of histamine and IL-6 from human mast cells stimulated by different triggers.[227] In another study comparing rupatadine to desloratadine and levocetirizine, rupatadine was shown to be superior at inhibiting PAF-induced release of histamine from human mast cells.[228]

Table 5. Histamine-1 Receptor Antagonists

Drug	***Characteristics***
• Bilastine	Nonsedating
• Cetirizine	Nonsedating
• Levocetirizine	Nonsedating
• Cyproheptadine	Antiserotonergic
• Diphenhydramine	Sedating
• Hydroxyzine	Anxiolytic
• Ketotifen	Anti-eosinophilic
• Loratadine	Nonsedating
• Desloratadine	Nonsedating
• Mizolastine	Nonsedating
• Rupatadine	Nonsedating, anti-PAF, mast cell inhibitor
Tricyclic Antidepressants	
• Amitriptyline (Elavil)	Weight gain
• Doxepin	Also H2 receptor antagonist
Phenothiazines	
• Promethazine	Antiemetic
• Prochlorperazine	Antiemetic

As discussed earlier, many patients with CSU do not respond to antihistamines (**Table 4**). For such patients, the anti-IgE omalizumab may be an appropriate treatment option.[229]

Conclusion

Mast cells have useful physiologic functions,[231] and play a critical role in atopic diseases,[11] especially allergies[38] and anaphylactic reactions,[2,4,11,231] as well as inflammation.[2,128,230,232,233] Given the multiple pathways involved in CSU, the possession of potent anti-PAF, anti-eosinophilic and mast cell inhibitory properties by rupatadine, makes it an excellent first-line drug for this debilitating condition.

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