The Critical Role of Mast Cells in Allergy and Inflammation

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ABSTRACT: Mast cells are well known for their involvement in allergic and anaphylactic reactions, but recent findings implicate them in a variety of inflammatory diseases affecting different organs, including the heart, joints, lungs, and skin. In these cases, mast cells appear to be activated by triggers other than aggregation of their IgE receptors (FcεRI), such as anaphylatoxins, immunoglobulin-free light chains, superantigens, neuropeptides, and cytokines leading to selective release of mediators without degranulation. These findings could explain inflammatory diseases, such as asthma, atopic dermatitis, coronary inflammation, and inflammatory arthritis, all of which worsen by stress. It is proposed that the pathogenesis of these diseases involve mast cell activation by local release of corticotropin-releasing hormone (CRH) or related peptides. Combination of CRH receptor antagonists and mast cell inhibitors may present novel therapeutic interventions.

KEYWORDS: asthma; coronary artery disease; inflammation; dermatoses; mast cells; skin; stress; vascular permeability

SELECTIVE RELEASE OF MAST CELL MEDIATORS

Mast cells are necessary for the development of allergic reactions, through cross-linking of their surface receptors for IgE (FcεRI),[1,2] leading to degranulation and the release of vasoactive, proinflammatory, and nociceptive

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mediators that include histamine, IL-6, IL-8, PGD_2, tryptase, and vascular endothelial growth factor (VEGF).[3–5] Mast cells derive from a distinct precursor in the bone marrow[6,7] and mature under local tissue microenvironmental factors.[5] In addition to stem cell factor (SCF), mast cell chemoattractants include nerve growth factor (NGF),[8] RANTES, and monocyte chemoattractor protein 1 (MCP-1).[9] They can secrete a multitude of biologically potent mediators (TABLE 1), giving rise to speculations about their possible role in innate or acquired immunity.[5,10,11] In addition to allergic triggers, mast cells can be activated by anaphylatoxins, antibody light chains, bacterial and viral antigens, cytokines, and neuropeptides.[12] Immunoglobulin-free light chains appear to elicit immediate hypersensitivity-like responses[13,14] through mast cell activation and subsequent induction of T-cell-mediated immune responses[15] (TABLE 2). Increasing evidence also indicates that mast cells are critical for the development of inflammatory diseases, especially in the pathogenesis of diseases such as arthritis, asthma, chronic dermatitis, and coronary artery disease (CAD) (TABLE 3).[12] However, unlike the case in allergic reactions, mast cells are rarely seen to degranulate during autoimmune[16] or inflammatory processes.[17] The only way to explain mast cell involvement in nonallergic processes would be through "differential" or "selective" secretion of mediators[18] without degranulation.[19] In fact, this may be the only way this ubiquitous and versatile cell may regulate immune responses without causing anaphylactic shock.

Instead, mast cells can undergo ultrastructural alterations of their electron-dense granular core, indicative of secretion, but without degranulation, a process that has been termed "activation,"[20–22] "intragranular activation,"[23] or "piecemeal" degranulation.[24] During such processes, mast cells can release many mediators *selectively* (TABLE 4)[25–27] as shown for serotonin[18] and eicosanoids.[28–30] Triggers include innate molecules, such as stem cell factor (SCF), which releases IL-6.[31–34] IL-1 can also stimulate human mast cells to release IL-6 selectively through 40–80-nm vesicles unrelated to the secretory granules (800–1000 nm).[35] Corticotropin-releasing hormone (CRH) can stimulate selective release of VEGF without degranulation.[36]

SKIN INFLAMMATION

Mast cells are well known for their role in skin hypersensitivity reactions.[37–41] Skin mast cells are located close to sensory nerve endings[42] and can be triggered by neuropeptides,[43–46] such as neurotensin (NT),[47] nerve growth factor (NGF),[48] substance P (SP),[49] and pituitary adenylate cyclase activating polypeptide (PACAP), all of which can be released from dermal neurons.[50] In fact, skin mast cells contain SP,[51] while cultured mouse and human mast cells were shown to contain and secrete NGF.[52]

Skin appears to have its own equivalent of the hypothalamic–pituitary–adrenal (HPA) axis,[53,54] the main regulator of which, CRH and its receptors,

TABLE 1. Mast cell mediators

Mediators	Main pathophysiologic effects
Prestored	
Biogenic amines	
Histamine	Vasodilation, angiogenesis, mitogenesis, pain
5-Hydroxytryptamine (5-HT, serotonin)	Vasoconstriction, pain
Chemokines	
IL-8, MCP-1, MCP-3, MCP-4, RANTES	Chemoattraction and tissue infiltration of leukocytes
Enzymes	
Arylsulfatases	Lipid/proteoglycan hydrolysis
Carboxypeptidase A	Peptide processing
Chymase	Tissue damage, pain, angiotensin II synthesis
Kinogenases	Synthesis of vasodilatory kinins, pain
Phospholipases	Arachidonic acid generation
Tryptase	Tissue damage, activation of PAR, inflammation, pain
Peptides	
Corticotropin-releasing hormone (CRH)	Inflammation, vasodilation
Endorphins	Analgesia
Endothelin	Sepsis
Kinins (bradykinin)	Inflammation, pain, vasodilation
Somatostatin (SRIF)	Anti-inflammatory action
Substance P (SP)	Inflammation, pain
Vasoactive intestinal peptide (VIP)	Vasodilation
Urocortin	Inflammation, vasodilation
Vascular endothelial growth factor (VEGF)	Neovascularization, vasodilation
Proteoglycans	
Chondroitin sulfate	Cartilage synthesis, anti-inflammatory action
Heparin	Angiogenesis, nerve growth factor stabilization
Hyaluronic acid	Connective tissue, nerve growth factor stabilization
De novo synthesized	
Cytokines	
Interleukins (IL)-1,2,3,4,5,6,9,10,13,16	Inflammation, leukocyte migration, pain
INF-γ; MIF; TNF-α	Inflammation, leukocyte proliferation/activation
Growth factors	
CSF, GM-CSF, b-FGF, NGF, VEGF	Growth of a variety of cells
Phospholipid metabolites	
Leukotriene B_4 (LTB_4)	Leukocyte chemotaxis
Leukotriene C_4 (LTC_4)	Vasoconstriction, pain
Platelet-activating factor (PAF)	Platelet activation, vasodilation
Prostaglandin D_2 (PGD_2)	Bronchonstriction, pain
Nitric oxide (NO)	Vasodilation

ABBREVIATIONS: TNF-α: tumor necrosis factor-α; INFγ: Interferon-γ; MIF: macrophage inflammatory factor; GM-CSF: granulocyte monocyte-colony stimulating factor; b-FGF: fibroblast growth factor; NGF: nerve growth factor; SCF: stem cell factor; VEGF: vascular endothelial growth factor.

TABLE 2. Mast cell triggers

Antigen + IgE
Anaphylatoxins
CRH
IL-1
Immunoglobulin-free light chains
LPS
NGF
NT
SCF
SP
Superantigens
Ucn
VIP
Viral DNA sequences

ABBREVIATIONS: CRH: corticotropin-releasing hormone; IL: interleukin; LPS: lipopolysaccharide; NGF: nerve growth factor; NT: neurotensin; SCF: stem cell factor; SP: substance P; Ucn: urocortin; VIP: vasoactive intestinal peptide.

are present in the skin.[55] Acute stress releases CRH in the skin,[56] inducing a local response.[54] Acute stress also induces redistribution of leukocytes from the systemic circulation to the skin[57]; it also exacerbates skin delayed hypersensitivity reactions[58] and chronic contact dermatitis in rats, an effect that depends on mast cells and CRH-1 receptors (CRHR-1).[59]

Computer-induced stress enhanced allergen-specific responses with concomitant increase in plasma SP levels in patients with atopic dermatitis.[60] Similar findings with increased plasma levels of SP, VIP, and NGF, along with a switch to a TH2 cytokine pattern, were reported in patients with atopic dermatitis playing video games.[61] Exercise was also shown to increase the

TABLE 3. Inflammatory diseases involving mast cells

Disease	Pathophysiologic effects
Asthma	Bronchonstriction, pulmonary inflammation
Atopic dermatitis	Skin vasodilation, T-cell recruitment, inflammation, itching
Coronary artery disease	Coronary inflammation, myocardial ischemia
Chronic prostatitis	Prostate inflammation
Chronic rhinitis	Nasal inflammation
Fibromyalgia	Muscle inflammation, pain
Interstitial cystitis	Bladder mucosal damage, inflammation, pain
Migraine	Meningeal vasodilation, inflammation, pain
Multiple sclerosis	Increased blood–brain barrier permeability, brain inflammation, Demyelination
Neurofibromatosis	Skin nerve growth, fibrosis
Osteoarthritis	Articular erosion, inflammation, pain
Rheumatoid arthritis	Joint inflammation, cartilage erosion

TABLE 4. Selective release of mast cell mediators

Stimuli	MC type	Mediators released	Mediators not released	Physiological importance	References
Endogenous					
IL-1β	RPMC	NO	PAF, H	Inflammation	194
PGE_2	RPMC	IL-6	H, TNF-α	Cytoprotection	195
SCF	BMMC	IL-6	H, LTC_4, TNF-α	MC development	33
IL-12	RPMC	INF-γ	H	Th1 immunity	196
CD8 ligands	RPMC	TNF-α, NO	H	T cell interaction	197
Thrombin	BMMC	IL-6	5HT, TNF-α	Anticlotting	198
SCF	hCBMC	IL-8	H, GM-CSF, INF-γ, IL-1β	Endothelial transmigration	199
Monomeric IgE	BMMC	IL-6	H, LTC_4	MC survival	200
Endothelin-1 -3	RMMC	TNF-α, IL-12↑	IL-4, IL-10, IL-13↓*	Th1 immunity	201
LTC_4/LTD_4	IL-4-primed hCBMC	TNF-α, MIP-1α, IL-5	H	Non-IgE mediated inflammation	202
IL-1	hCBMC	IL-6, IL-8, TNF	H, tryptase	Inflammation	35
CRHR-1	hCBMC	VEGF	H, tryptase, IL-8	Inflammation	77
CRHR-2	hCBMC	IL-6	H, tryptase, IL-8, VEGF	Inflammation	203
Exogenous/ Pharmacological					
Amitriptyline	RPMC	Serotonin	H	Headaches	18
LPS	RPMC	IL-6	H	Bacterial infection	31
CpG DNA	BMMC	TNF-α, IL-6	HA, IL-4, IL-12, GM-CSF, INF-γ	Host response to bacteria	204
Cholera Toxin	RPMC	IL-6	H, TNF-α	Inflammation	205
PMA	BMMC	VPF/VEGF	5HT	Angiogenesis	4
Clostridium difficile toxin A	RPMC	TNF-α	H	GI tract inflammation	206
H. pylori VacA toxin	BMMC	IL-6, IL-8, TNF-α	H	Gastric injury	150
Suboptimal FcεRI stimulation	BMMC	MCP-1	IL-10, H	Chemokines ≫cytokines /H	207
S.a. peptidoglycan or zymosan	hCBMC	GM-CSF, IL-1β, RANTES, LTC_4	β-hexosaminidase, IL-6	Exacerbation of asthma by bacterial infection	141

ABBREVIATIONS: BMMC: bone marrow mast cells; CRHR: corticotropin-releasing hormone; H: histamine; hCBMC: human cord blood mast cells; LPS: lipopolysaccharide; LTC_4: leukotriene C_4; PMA: phorbol myristate acetate; TNF-α: tumor necrosis factor-α; NO: nitric oxide; MIP: macrophage inhibitory protein; GM-C5F: granulocyte monocyte-colony stimulating factor; 5HT: 5-hydroxytryptamine; INF-γ: interferon-γ; MCP-1: monocyte chemoattractant protein-1; RMMC: rat mucosal mast cells; RPMC: rat peritoneal mast cells; VPF: vascular proliferating factor; MC: mast cells; IgE: immunoglobulin E; SCF: stem cell factor; GI: gastrointestinal.

responsiveness of skin mast cells to morphine only in patients with exercise-induced asthma.[62]

CRH[63] and its structurally related peptide, urocortin (Ucn),[64] can activate skin mast cells and induce mast-cell-dependent vascular permeability in rodents. CRH also increases vascular permeability in human skin,[65] a process dependent on mast cells. CRH-R2 receptor expression was shown to be up-regulated in stress-induced alopecia in humans,[66] CRH-R2 expression was increased in chronic urticaria.[67] Acute restraint stress induces rat skin vascular permeability,[68] an effect inhibited by a CRH receptor antagonist and absent in mast-cell-deficient mice.[63,64]

Proteases released from mast cells could act on plasma albumin to generate histamine-releasing peptides,[69,70] which would further propagate mast cell activation and inflammation. Proteases could also stimulate protease-activated receptors (PARs), inducing microleakage and widespread inflammation.[71,72] Many dermatoses, such as atopic dermatitis (AD), chronic urticaria, and psoriasis, are triggered or exacerbated by stress,[73] which also worsens eczema[74] and acne vulgaris.[75]

Mast cells are localized close to CRH-positive neurons in the median eminence[76] and express functional CRH receptors.[77] The median eminence is rich in mast cells[78,79] and contains most of the histamine in the brain.[80] Hypothalamic mast cell activation can stimulate the HPA axis.[81–83] Histamine is considered a major regulator of hypothalamus[84] and can increase CRH mRNA expression there.[85] Moreover, human mast cells can synthesize and secrete large amounts of CRH[86] as well as IL-1 and IL-6, which are independent activators of the HPA axis.[87] The immunoendocrine responses to stress in chronic skin inflammatory diseases have been reviewed,[12,88] and it was proposed that mast cells constitute the "sensor" of a "brain–skin" connection.[89]

INFLAMMATORY ARTHRITIS

The presence of mast cells in joints has been known for many years.[17,90–96] Moreover, fluid aspirated from joints of patients with arthrosynovitis contains RANTES and MCP-1,[97] both of which are potent mast cell chemoattractants.[9] Mast cells are required for autoimmune arthritis[98] and inflammatory arthritis,[99] as knee involvement was absent in the joints of W/W^v mast cell–deficient mice as compared to their +/+ controls. Inflammatory arthritis was also significantly reduced in CRH knockout mice[99] and in mice treated with the CRH receptor-1 antagonist, Antalarmin.[100]

Mast cells in the joints of rheumatoid arthritis (RA) patients express CRH receptors.[101] Moreover, CRH,[101,102] Ucn,[103,104] and CRH receptors are increased in the joints of inflammatory and RA patients, the symptoms of whom worsen by stress.[105,106]

ASTHMA

Asthma is one of the most common chronic illnesses, affecting roughly 300 million people worldwide.[107,108] The morbidity and mortality due to asthma continues to increase despite advances in both our scientific knowledge, as well as in hygiene and drugs for this disease.[108] The World Health Organization has estimated that 1 of 250 deaths worldwide is due to asthma. These facts highlight the need for an improved understanding of the cellular and molecular mechanisms that contribute to the pathogenesis of asthma.

Recent reports indicate that stress can exacerbate asthma.[109–114] One study indicated that maternal stress may be responsible for the subsequent cellular response in childhood asthma.[115] It has been postulated that stress associated with urban living may contribute to poor asthma control.[116] Stress has long been postulated to have a negative impact on asthma, but the mechanisms by which this occurs remain poorly defined.[109,111,112,114,117,118] One study showed that adolescents with asthma in a low socioeconomic group, who reported more stressful and acute life events, had more asthma exacerbation and higher serum Th-2 cytokines than those in higher socioeconomic status.[119] The Inner City Asthma Study showed a correlation between community violence and asthma morbidity.[120] Post-traumatic psychological stress following the 9/11 attacks on the World Trade Center correlated with increased symptom severity in subjects with moderate-to-severe asthma and with utilization of urgent care in New York City.[121,122] In an epidemiological study carried out among 10,667 Finnish first-year university students (18–25 years old), it was shown that an excess of stressful events, such as concomitant severe disease or death of immediate family members or family conflicts, were associated with exacerbation of asthma.[111]

Stress associated with final examinations, as compared to mid semester, of college students with mild asthma increased sputum eosinophil counts, as well as eosinophil-derived neurotoxin and IL-5 once the eosinophils were cultured for up to 24 h.[117] It was suggested that a shift in cytokine generation to that of a Th2 type may be the defining parameter.[113] In one longitudinal study of 92 adults with asthma, it was determined that subjects who reported more negative life events and had low levels of social support had more episodes of asthma exacerbation induced by upper respiratory tract infections.[123] A large prospective long-term follow-up community-based cohort study of young adults showed a dose–response relationship between panic and asthma.[124] In fact, one study indicated that maternal stress may be responsible for the cellular response in childhood asthma,[115] while another showed that greater levels of caregiver-perceived stress at 2–3 months was associated with increased risk of subsequent repeated wheezing among children during the first 14 months of life.[125] Such findings cannot be easily explained as the HPA axis apparently functions normally in asthmatic adult patients, producing appropriate plasma cortisol

increases in response to stress[126] which might be expected to reduce rather than exacerbate asthma symptoms. One publication showed a significantly blunted cortisol response to stress only in asthmatic children,[127] suggesting there may be differences due to age.

While no animal model exactly replicates human asthma, the use of animals has provided helpful information about the mechanisms of airway inflammation and hyperreactivity seen in asthma.[128,129] Chronic exposure to aerosolized ovalbumin has been shown to be a useful murine model of asthma leading to airway inflammation, airway hyperresponsiveness (AHR),[130] as well as microvascular leakage in the airways.[130–132] Microvascular leakage in the airway wall may also be important for the airway wall remodeling that is found in most asthmatics.[133,134] More recently, the house dust mite allergen model has been shown to effectively induce chronic airway inflammation and AHR.[133,135] Stress has been shown to increase AHR[114] and inflammation[114,136] in response to ovalbumin challenge in murine models of asthma. In one case, exposure to an ultrasonic stressor, coinciding with the first aerosol challenge, significantly increased allergen-induced pulmonary reactivity and bronchial inflammation. Short-term (3 days) stress before allergen challenge decreased the number of inflammatory cells, but increased IL-6, while long-term (7 days) stress evidently increased the number of inflammatory cells but did not alter IL-6 levels.[136]

The role of mast cells in asthma is undisputed.[137–139] Rodent mast cells express bacterial Toll-like receptors (TLRs) 2 and 4.[140,141] However, the pattern of response may be species- and tissue-specific, making generalizations difficult. TLRs were initially discovered in *Drosophila* as the receptors responsible for dorso-ventral patterning in the developing embryo; however, soon after they were shown to be important in the development of innate immunity to invading pathogens.[142] Subsequently, human homologues for TLRs were identified beginning with TLR-4, which was shown to bind lipopolysaccharide (LPS). Ten human TLRs have been identified so far.[143–145] Evidence is building that TLRs play an important role in recognition of ligands associated with bacterial or viral infections, and play a key role in the development of adaptive immune responses,[144] especially in asthma.[146] LPS induced release of TNF-α through TLR-4, while peptidoglycan induced histamine release through TLR-2 from rodent mast cells. Fetal rat skin-derived mast cells expressed TLR-3, 7, and 9 and activation by CPG oligodeoxynucleotide induced release of TNF and IL-6, as well as RANTES and MIP, but without degranulation.[147,148] In another paper, LPS could not induce release of GM-CSF, IL-1, or LTC_4.[141] However, LPS did induce secretion of TH2 cytokines IL-5, IL-10, and IL-13 and increased their production by FcεRI cross-linking.[149] Elsewhere, it was shown that TLR-2 activation produced IL-4, IL-6, and IL-13, but not IL-1,[150] while LPS produced TNF, IL-1, IL-6, and IL-13, but not IL-4 or IL-5, without degranulation.[150] Activation of these receptors even in human cultured mast cells leads to distinct biological effects: Human mast cells express viral TLR-9,[151]

activation of which produced the proinflammatory cytokine IL-6,[151] while they produced IFN in response to double-stranded RNA through TLR-3.[152] These findings may explain how viral infections worsen asthma.

Viral infections have been shown to exacerbate asthma and contribute to as many as 50% of asthma-associated deaths; moreover, more than 80% of childhood asthma exacerbations are associated with viral airway infections.[153] A number of studies have shown that viral infections increase airway hyperresponsiveness and antigen sensitization,[154] as well as recruitment of inflammatory cells.[155] Synoptical virus, metapneumovirus, rhinovirus, adenovirus,[156] as well as influenza and parainfluenza virus have been implicated in the pathogenesis of asthma.[157–159] In fact, rhinovirus infections during infancy appear to predict childhood wheezing,[160] while respiratory syncytial virus during the first 3 months of life was shown to promote a TH2 response, especially significantly high levels of IL-4.[161] Such early-infancy viral respiratory infections may also induce metalloproteinases, which are involved in airway remodeling in asthma.[162] However, this field is quite confusing because current discussions focus on viral nucleic acid inoculation.[163]

CORONARY INFLAMMATION

Increasing evidence implicates acute psychological stress and cardiac mast cells in coronary artery disease (CAD), especially when it occurs without angina, which appears to involve a sizable portion of myocardial infections (MI).[164–167] Cardiac mast cells can participate in the development of atherosclerosis, coronary inflammation, and cardiac ischemia.[168] Mast cells are particularly prominent in coronary arteries during spasm[169] and accumulate in the shoulder region of human coronary plaque rupture.[170–172] The human mast cell proteolytic enzyme chymase is the main cardiac source of converting enzyme that generates the coronary constrictor angiotensin II;[173] the chymase can also induce the removal of cholesterol from HDL particles and uptake by macrophages that become "foam" cells, major components of coronary atheromas.[174–177] Cardiac mast-cell-derived histamine[178] can constrict the coronary arteries[179] and can sensitize nerve endings;[180] this is particularly important because mast cells are localized close to nerve endings in atherosclerotic coronary arteries.[181]

Acute stress induces rat cardiac mast cell activation, an effect blocked by the "mast cell stabilizer" disodium cromoglycate (cromolyn).[182] Acute stress can also induce histamine release from mouse heart,[183] as well as increase serum histamine and IL-6.[183,184] These effects are dependent on mast cells and are greater in apolipoprotein E (ApoE) knockout mice that develop atherosclerosis.[183,184] Serum IL-6 elevations in patients with acute CAD were documented to derive primarily from the coronary sinus.[185] Both histamine[186] and

IL-6[187] are significant independent factors of CAD morbidity and mortality. There are also reports of anaphylactic CAD that has been termed the "Kounis" syndrome.[188,189]

CONCLUSION

Mast cells have emerged as unique immune cells that can be activated by many immune and nonimmune triggers, including acute stress through CRH; it is, therefore, proposed that CRH be renamed SRH (**Stress Response Hormone**) to reflect its versatile role in stress. Mast cells are critical in the development of inflammatory diseases, especially dermatoses, asthma, arthritis, and CAD. Inhibition of mast cell activation by CRH,[190] therefore, is a novel target for the development of new treatments for inflammatory and autoimmune disorders. Certain dietary supplements have recently been shown to be effective in this regard[191] because they combine the proteoglycan chondroitin sulfate[192] and the flavonoid quercetin,[193] both of which have mast cell inhibitory and anti-inflammatory actions.

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