

Mast Cell Mediators in Allergic Inflammation and Mastocytosis

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Human mast cells originate from CD34-expressing multipotent hematopoietic progenitors in the bone marrow [1] and are home to most organs, where they localize predominantly around blood vessels [2,3]. Mast cells preferentially populate tissues in contact with the external environment, including the respiratory and gastrointestinal tracts and the skin [4–6]. Parenchymatous organs, such as the heart, brain, liver, spleen, lymph nodes, and genitourinary tract, possess fewer mast cells, the number of which increases in patients with mastocytosis [7,8]. Mast cells are rarely found in peripheral blood, and their recognition in tissues is facilitated by the metachromatic properties of their granules, which stain purple with toluidine blue dye [9]. Nonmetachromatic CD34-expressing circulating committed progenitors give rise to in situ human and mice tissue mast cells [10]. Functional and phenotypic heterogeneity exists among distinct mast cell populations at different tissue locations. Resident connective tissue mast cells from the skin and gastrointestinal and respiratory submucosa express mast cell tryptase, chymase, and carboxypeptidase A in their granules (MCTc), which contain gratings and lattice structures [6,11]. These mast cells release mediators in response to antigen, anti-IgE, calcium ionophore A23187, compound 48/80, morphine sulfate, formyl-met-leu-phe (fMLP) peptide, substance P, and anaphylotoxins (eg, C5a, C3a) [12]. Reactive mast cells found at the mucosal surfaces of the gastrointestinal and respiratory tracts express only mast cell tryptase (MCT); have scrolls in their granules; and release mediators in

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response to antigen, anti-IgE, and calcium ionophore A23187 but not to anaphylotoxins or other nonimmunologic stimuli [13,14]. Some mast cells in the intestinal submucosa and salivary glands are distinct from classic mucosal and connective tissue mast cells in that they contain only mast cell chymase in their granules (MCCs) [15]. Human and mouse mast cell development and differentiation depend on the interactions between the hematopoietic growth factor stem cell factor (SCF) expressed on the surface of and secreted by fibroblasts and stromal cells and its receptor, the tyrosine kinase c-kit, a proto-oncogene highly expressed on the surface membrane of all mature and immature mast cells [16–20]. Exposure of nonmetachromatic mast cell progenitors from fetal liver, cord blood, bone marrow, or peripheral blood to SCF for several weeks results in mast cell development *in vitro* [10,21]. Mast cell deficiency is seen in mice with a mutated W or Sl locus, coding for the c-kit receptor and for SCF, respectively [22]. Factors like thrombopoietin, interleukin (IL)-9, IL-16, and nerve growth factor (NGF) stimulate the *in vitro* growth of human mast cells, whereas IL-4, retinoids, and interferon- γ (IFN γ) decrease the number of developing mast cells in response to SCF [23].

Finding increased numbers of mast cells in the nasal mucosa of patients with allergic rhinitis [24], in the smooth muscle of patients with asthma [25], in the skin of patients with urticaria [26], and in the joints of patients with arthritis [27] illustrates the participation of mast cells in rhinitis, asthma, urticaria, and arthritis. Mast cell mediators, including tryptase and histamine, are found elevated in nasal secretions [28], bronchoalveolar lavage (BAL) fluid [29], skin [30], and joint fluid [31] in patients presenting with these diseases, providing evidence that mast cell activation has a fundamental role in their pathogenesis. In contrast to the apparent detrimental role of mast cells in inflammatory and allergic disease, mast cells have been found to have a protective role in innate immunity. In a mouse model of experimental bacterial peritonitis, W/W^v mast cell-deficient mice can be rescued from death by mast cell reconstitution and by tumor necrosis factor (TNF)- α , a cytokine secreted by activated mast cells [32,33]. In a model of parasite infection, the physiologic mast cell hyperplasia in response to the helminthic worm burden is abrogated with SCF blocking antibodies, with a dramatic delay in worm expulsion [34]. Immunologic (IgE cross-linking of the high-affinity receptor for IgE [35], Fc ϵ receptor (Fc ϵ R) I, and IgG cross-linking of the low-affinity receptor for IgG, Fc γ receptor (Fc γ R) III, [36] and the high-affinity receptor for IgG, Fc γ RI) [37,38] and nonimmunologic (complement [39], chemokines [40], and Toll-like receptors [TLRs] [41]) activation results in the release of mediators from mast cells. Preformed granule mediators, such as histamine, neutral proteases, preformed cytokines, and proteoglycans, are released by exocytosis within minutes [42–44]. Although the synthesis of lipid membrane-derived arachidonic acid (AA) metabolites also occurs within minutes and includes prostaglandins (PGD₂) [45] and leukotrienes (LTB₄ and LTC₄) [46], the activation of inflammatory chemokine and cytokine

genes occurs later, and their products are released within hours of an activating stimulus [47–49].

The recognition of mast cell and mast cell mediator participation in angiogenesis, cardiovascular diseases, and tumor growth has renewed interest in the study of mast cells and the products of their mediators. The purpose of this review is to summarize current knowledge of mast cell mediators and their actions on known diseases and to anticipate their potential participation in mast cell activation syndromes and mastocytosis.

Secretory granules

Histamine

Histamine is an amine produced by the decarboxylation of histidine, and it is stored in the secretory granules of all mature mast cells including connective tissues, mucosal membranes, skin and basophils [50,51]. No differences are seen in the amounts of histamine stored in mast cells reflecting a similar mechanism for synthesis and storage [50,51]. Once released into circulation, histamine is metabolized by histamine methyl transferase after one pass through the system. Plasma histamine has a short half-life of less than 30 minutes and diurnal variations precluding its use as a marker for mast cell activation syndromes or mastocytosis [52]. The effects of histamine are mediated through H1, H2, H3, and H4 receptors [53–55]. H1 receptors control the tone and permeability of the vascular bed and the tone of the intestinal and bronchial smooth muscle. H1 receptors also mediate increases in mucus production and heart rate and flushing responses [56,57]. H2 receptors participate in the control of vascular permeability, gastric acid secretion, and airway mucus production [58]. Intravenous infusion of histamine into normal human subjects causes increased heart rate, diastolic hypotension, flushing, and headache, which resolve in only a few minutes after discontinuation of the infusion [59,60]. H3 receptors are located in the brain and have been implicated in locomotor activity and exploratory behavior in mice [58,61]. The newly described H4 receptor is a G-protein-coupled receptor (GPCR) with little homology with the H1 receptor expressed on mast cells [55]. A recently described selective H4 histamine receptor blocks histamine-induced chemotaxis, calcium flux in bone marrow mast cells (BMMCs), and the migration of tracheal mast cells from the connective tissues to the epithelium [54]. In vitro, H1 receptors enhance chemotaxis of human neutrophils and eosinophils, but H2 receptors are inhibitory of neutrophil and eosinophil influx [62,63]. Disruption of the sleep pattern and an abnormal somnolent behavior, as well as enhanced T helper (Th) 2 responses, are seen in mice lacking the H1 receptor [64–66].

Levels of plasma histamine were found to be significantly elevated in a cohort of patients with different mastocytosis disorders as compared with

controls [52]. Individual plasma histamine determinations have limited value in the diagnosis or management of patients with mastocytosis, however, because of diurnal variations, with levels overlapping the normal population [52]. Urinary histamine and its metabolites, methyl histamine and methylimidazole acetic acid, collected in 24-hour urine samples are elevated in patients with systemic mastocytosis (SM) but not in patients with cutaneous mastocytosis [67]. These metabolites are elevated during asymptomatic periods in patients with SM but are further increased during acute episodes of flushing, systemic vasodilation, and vascular collapse. These metabolites are also elevated in patients presenting with acute mast cell activation induced by allergen exposure, such as that seen during anaphylaxis [68]. Increases in urinary methylimidazole acetic acid can also be found in association with myeloproliferative disorders and after ingestion of processed foods with high histamine content (eg, cheese, cured meats).

Proteases

On a weight and molar basis, proteases active at neutral pH are the major protein constituents of human mast cell granules and are exocytosed after mast cell activation or released on a chronic basis, as is seen for tryptase in patients with mastocytosis [69]. Although progress has been made in defining the functions of mast cell proteases, the biologic substrates and plasma inhibitors have not been defined for all of them. Tryptases, chymases, and carboxypeptidase A represent the three major families of proteases stored in the secretory granules of human mast cells [70]. Tryptases have been discussed in detail elsewhere in this issue by Schwartz, and therefore are not covered in this review.

Chymase

Human chymase is a chymotrypsin-like serine endopeptidase of 30 kDa encoded on chromosome 14 and originally purified from human skin [71]. Antibodies raised against skin chymase have localized the enzyme in mast cells from skin and connective tissues, including the submucosa of lung and gastrointestinal tracts [50]. Like tryptase, chymase is stored in mast cell secretory granules in an active form and is bound to proteoglycans [11]. Chymase is inhibited by plasma proteinase inhibitors, and plasma localization after mast cell activation has not been reported in people but does occur during helminthic infection with adult worm expulsion in the mouse and the rat [70]. Chymase cleaves activation peptides ending in acidic amino acid residues and converts angiotensin I to the vasoconstrictive peptide angiotensin II in a similar fashion as the angiotensin-converting enzyme (ACE) [72]. In vitro, chymase can also cleave laminin, type IV collagen, and fibronectin and can activate the metalloproteinase (MMP)-2 and the IL- β precursor [73]. Mast cells from patients with mastocytosis express chymase

in skin lesions of urticaria pigmentosa and in the bone marrow of patients with systemic involvement [74].

Carboxypeptidase A

Human mast cell carboxypeptidase A (MC-CPA) belongs to the family of metalloexopeptidases (CPA and CPB) and was originally purified from lung and skin mast cells as a 32-kDa zinc-containing enzyme [75]. The gene is located on chromosome 3 [76]. The gene structure of MC-CPA is similar to that of MC-CPB, but the substrate specificity of the active site closely resembles that of bovine pancreatic CPA [77,78]. MC-CPA is stored in granules along with tryptase and chymase and is released on mast cell activation: plasma localization has not been reported. MC-CPA cleaves carboxy (COOH)-terminal aromatic and aliphatic amino acid residues, converting angiotensin I to angiotensin II. In addition, MC-CPA can cleave bradykinin and substance P [37,79].

Human MC-CPA is not expressed by other hematopoietic lineages. By immunochemistry, the enzyme is present in mast cells in the skin and gut and lung submucosa [74]. CPA is found in urticaria pigmentosa skin lesions and in tissue mast cells in the lymph node, spleen, liver, and bone marrow of patients with cutaneous and SM [74]. Highly immature nonmetachromatic circulating mast cells from a patient with aggressive mastocytosis expressed CPA along with tryptase but not chymase [9].

Proteoglycans

Human mast cells contain heparin and chondroitin sulfate proteoglycans that stabilize and regulate secretory granule proteases [44]. Constitutive mast cells of mice with targeted disruption of a gene essential to heparin glycosaminoglycan biosynthesis failed to express and store specific proteases and presented only a few, small, abnormal granules [80]. Heparin proteoglycan is released from mast cell granules along with proteases and histamine during mast cell activation [81]. The tight ionic interactions between proteases and heparin proteoglycan attenuate the diffusion of exocytosed proteases into the connective tissue, and only proteins with less charge at neutral pH can progress to the vascular bed [82,83].

Heparin binds to antithrombin III, which prevents the activation of the clotting cascade. Heparin binding regulates and stabilizes cytokines, chemokines, and growth factors, including fibroblast growth factor (FGF)-2, which is involved in angiogenesis and wound healing [84].

With few exceptions, patients with cutaneous mastocytosis or SM are not at increased risk for hemorrhagic complications [85,86], and heparin levels are not detected in the circulation [87,88], except during severe episodes of vascular collapse [87]. Patients with SM presenting with hemorrhagic ulcer disease have an elevated thrombin clotting time correctable with protamine,

indicating increased heparin activity. In pediatric patients with skin bullous disease, severe bleeding of skin lesions has been reported [89].

Membrane-derived lipid mediators

Human mast cells generate and release eicosanoid lipid mediators through a transmembrane activation signal with calcium influx [45,90]. Prostaglandins and leukotrienes are metabolic products of AA derived from membrane phospholipids through the action of phospholipase enzymes (eg, PLA2) [91]. Other products of AA include hydroxyeicosatetraenoic acids (HETEs), lipoxins, epoxyeicosatrienoic acids, and isopropanes, which contribute to modulate inflammatory responses [92]. Cytosolic (type IV) PLA2 is involved in the generation of all eicosanoids, including prostaglandins, thromboxanes, prostacyclins, and leukotrienes. Secretory PLA2 released from secretory granules can bind to the cell surface through heparan sulfate proteoglycans and amplify the biosynthesis of prostaglandin [93,94]. Activation of BMMC through c-kit or FcεRI elicits two phases of eicosanoid generation: an immediate granule exocytosis completed in 10 minutes and associated with the synthesis of LTC4 and PGD2 [43,94] and a delayed phase 2 to 10 hours after activation, followed by the release of PGD2 alone [95]. During the acute phase, the generation of PGD2 is dependent on constitutively expressed cyclooxygenase (COX)-1, in contrast to the delayed phase, which is dependent on the induced expression of COX-2 [96].

Prostaglandins: prostaglandin D2

Human mast cells isolated from different tissues have substantial capacity to generate PGD2 and a wide variation in the production of the cysteinyl (Cys) leukotrienes, as assessed ex vivo after tissue dispersion and FcεRI-mediated activation [97].

Aspirin-sensitive prostaglandin endoperoxide synthase 1 and 2 (COX-1 and COX-2) isoenzymes catalyze the conversion of AA to PGH2 [98], and cell-specific terminal synthases convert PGH2 to the terminal prostanoid, such as PGD2, via PGD synthase in mast cells. After its synthesis by mast cells, PGD2 is released extracellularly by a prostaglandin transporter protein and binds to prostaglandin receptors on target cells, where it exerts its effects. PGD2 is metabolized to 15-dPGJ2 and to 9a, 11b-PGF2; the latter can be found in normal urine. Increased PGD2 and 9a, 11b-PGF2 measured by mass spectrometry is an index of mast cell activation and correlates with the histologic presence of SM [68,99]. Circulating levels of PGD2 and its major metabolite, 9a, 11b-PGF2, are found in patients with SM subject to vascular collapse [67] but also in individuals experiencing anaphylaxis.

PGD2 causes bronchoconstriction on inhalation, and when injected into the skin, it produces a wheal-and-flare response attributable to vasodilation and increased vasopermeability [100]. Flushing in response to niacin is

mediated by PGD2. Patients with asthma present with increased PGD2 in BAL at baseline, which is further increased after allergen challenge, indicating local mast cell activation [101]. PGD2 inhibits platelet aggregation.

Two PGD2-specific GPCRs have been characterized: DP1 and DP2 [102,103]. Human DP1 receptor is strongly expressed in the retina and small intestine, and human DP2 receptor is expressed in all tissues, with predominance in the brain, heart, stomach, adrenal gland, liver, small intestine, thymus, and placenta. Both receptors bind PGD2 with high affinity and signaling, although the DP1 receptor is associated with increased cyclic adenosine monophosphate (cAMP), whereas DP2 signaling is associated with decreased cAMP [104]. In vitro, PGD2 is a chemoattractant for eosinophils, basophils, dendritic cells, and Th2 lymphocytes through the DP2 receptor and potentiates the exocytosis of basophils. PGD2 controls the migration (through DP1) and maturation (through DP2) of dendritic cells, favoring a Th2 response [105]. Sensitized mice deficient in DP1 exhibit a decreased airway inflammatory response to allergen challenge, diminished production of Th2 cytokines in the lung, and diminished eosinophil accumulation relative to controls [106]. Transgenic mice overexpressing the PGD2 synthase gene and producing increased levels of PGD2 in the brain have a significant increase in non-rapid eye movement (REM) sleep and a dramatic decrease in locomotor activity after tail clipping compared with controls [107]. PGD2 is found to regulate sleep patterns in rats [108], and cerebral spinal fluid PGD2 concentration has a circadian rhythm with increased levels during sleep deprivation [109].

Leukotrienes: leukotriene B4 and leukotriene C4

AA released by PLA2 is processed by 5-lipoxygenase (5-LO) in the presence of 5-lipoxygenase activating protein (FLAP) into hydroperoxyeicosatetraenoic acid (5-HPETE) and then to LTA4 [110]. LTA4 hydrolase catalyzes the formation of LTB4, and LTC4 synthase conjugates LTA4 to glutathione to form the CysLTC4. After carrier-mediated export, LTC4 is converted into the active metabolites LTD4 and LTE4 by cleavage removal of glutamic acid and then glycine [110,111]. The actions of CysLTC4, CysLTD4, and CysLTE4 are mediated through two distinct GPCRs: CysLT1 and CysLT2 [112,113]. The agonist potency of the CysLT1 in human bronchial smooth muscle is greater for LTD4 and LTC4 and lower for LTE4, and selective antagonists, such as montelukast, zafirlukast, and pranlukast, have been shown to be efficacious in asthma. CysLT2 has been found in human pulmonary and saphenous veins, and the agonist potency is similar for LTC4 and LTD4, with a weaker potency for LTE4 [112]. The CysLT1 receptor is highly expressed on normal lung muscle cells; spleen; and peripheral blood leukocytes, including eosinophils, monocytes, macrophages, and CD34-positive precursors [114]. It is not expressed on normal airway epithelial cells. In nasal mucosa, the expression of CysLT1

is found on resident eosinophils, mast cells, macrophages, neutrophils, and vascular endothelial cells. A human cell line derived from a patient with human mast cell leukemia HMC-1 has been found to express CysLT1 mRNA and protein. The human CysLT2 receptor is strongly expressed in the human heart, adrenals, peripheral blood leukocytes, spleen, lymph nodes, and central nervous system (CNS). In the lung, its expression is found in interstitial macrophages, with weak expression on smooth muscle cells. Some of the CysLT2 receptor expression overlaps that of the CysLT1 receptor, but it is far more abundant and is distinctively expressed in the brain and cardiac Purkinje cells [115].

CysLTC4, CysLTD4, and CysLTE4 increase microvascular permeability and induce long-lasting wheal-and-flare responses in human skin [100,116]. On inhalation, LTC4 and LTD4 induce bronchoconstriction in normal subjects with a 1000-fold greater potency than histamine, whereas LTE4 is only 10-fold [117]. LTC4 caused a dose-response increase in calcium and chemotactic responses in human coronary smooth muscle cells. Human mast cells derived from cord blood-derived CD34-expressing progenitors respond to exogenous cysteinyl leukotrienes, including CysLTC4, with a strong calcium flux and phosphorylation of extracellular signal-related protein kinase, which is enhanced when the cells are primed with IL-4 [118]. The nucleotide uridine diphosphate (UDP)-induced calcium flux in IL-4-primed mast cells was blocked by a selective CysLT1 receptor antagonist, MK571, indicating cross-desensitization [119]. LTC4, LTD4, and UDP induced the generation of IL-5, TNF α , macrophage inflammatory protein (MIP)-1 β , and IL-8 in IL-4-primed human mast cells. CysLT1 inhibitor MK571 and FLAP inhibitor MK886 decreased IL-5 and TNF α production after Fc ϵ RI stimulation, implying autocrine signaling by cysteinyl leukotrienes in mast cells [120].

Urinary LTE4 (N-acetyl LTE4) is found to be elevated in patients with aspirin intolerance at baseline and increases further after aspirin challenge. Inhibitors of 5-LO block bronchoconstrictive responses to cold air and to aspirin challenge in asthmatic patients [121]. CysLT1 receptor antagonists are effective at attenuating early and late responses after allergen and exercise challenges [122] and, more importantly, are efficacious in the management of chronic bronchial asthma [123]. Targeted disruption of the mouse CysLT1 abrogated enhanced vascular permeability during inflammatory responses. No reported measurements of leukotrienes in patients with mastocytosis between or during clinical flares are available.

Platelet activation factor

Platelet activation factor (PAF) is produced by acetylation at the SN-2 position after PLA2 cleavage of arachidonate in membrane phospholipids [124] and is found in platelets, eosinophils, neutrophils, mast cells, endothelial cells, and epithelial cells. Human recombinant PAF induces shock and

death when injected intravenously in mice [125], and its effect is inhibited by PAF acetylhydrolase [126]. Mice lacking the PAF receptor have a significant reduction in this response [126].

Inhaled PAF causes bronchoconstriction and increased bronchial responsiveness in normal subjects and in asthmatics. PAF is 1000 times more potent than histamine at inducing increased vasopermeability in human beings [127]. PAF has been found to be elevated in skin in diffuse cutaneous mastocytosis [128].

Chemokines and cytokines

Human mast cells are a source of multifunctional cytokines, but little is known of the regulation and secretion of cytokines and chemokines by patients with mastocytosis. [129]. Preformed TNF α , found in human skin and pulmonary mast cell granules, is released after IgE-, IgG-, and TLR-mediated activation. High-density oligonucleotide probe arrays (GeneChip analysis) have permitted elucidation of the cytokine gene expression pattern after mast cells have been activated through Fc ϵ RI ligation and comparison with the expression through Fc γ R ligation and TLR4-receptor ligation [130]. Mast cells express nuclear factor (NF)- κ B-related genes and Th2 cytokines, such as IL-5 and IL-13, on Fc ϵ RI-mediated activation. Those include granulocyte (G) colony-stimulating factor (CSF), macrophage (M)-CSF, GM-CSF, IL-1 β , IL-3, IL-5, IL-6, IL-8, IL-10, IL-13, IL-16, IL-18, IL-22, TNF α , and NGF [131]. Specific Fc ϵ RI-mediated genes also include amphiregulin, epiregulin, and inhibitin b as well as chemokines, such as CCL-7 (monocyte chemoattractant protein [MCP]-3) and CCL-1 (eotaxin) [132]. Murine mast cells express TLR2 and TLR4 [133,134], and peptidoglycan from *Staphylococcus aureus* stimulates mouse BMMCs to produce TNF α , IL-4, IL-5, IL-6, and IL-13 in a TLR2-dependent fashion, resulting in mast cell degranulation and calcium mobilization. *Escherichia coli*-derived lipopolysaccharide (LPS) stimulates mast cell production of TNF α , IL-1 β , IL-6, and IL-13 through activation of the TLR4 receptor. The reconstitution of W/W^v mice by transfer of TLR4-deficient BMMCs in a model of acute sepsis resulted in significantly higher mortality because of defective neutrophil recruitment and production of proinflammatory cytokines [135]. Cord blood-derived human mast cells express mRNA for TLR1, TLR2, and TLR6 but not for TLR4; however, peripheral blood-derived human mast cells express TLR4 [136]. Bacterial peptidoglycan and yeast zymosan in those cells induced GM-CSF, IL-1 β , and substantial CysLT generation through TLR2/TLR6 activation. Stimulation of mast cells through TLR4 induces the expression of IL-12 [129].

Fc γ RIII receptors are found on murine mast cells and induce IgG- and immune complex-dependent degranulation and mediator release, including anaphylaxis [137]. Human mast cells express the high-affinity IgG receptor Fc γ RI and a low-affinity IgG receptor, Fc γ RII, but no Fc γ RIII [38].

In vitro, IFN γ upregulates the expression of Fc γ RI and TLR4, and the aggregation of Fc γ RI results in exocytosis with the release of histamine, PGD₂, and LTC₄ [37]. Proinflammatory cytokines, such as TNF α and IL-1 β , are more upregulated by Fc γ RI than by Fc ϵ RI. The production of TNF α in response to aggregation of Fc γ RI and via TLR4 is two- to sixfold higher than that induced by Fc ϵ RI aggregation [129].

Proinflammatory mediators

TNF α was the first cytokine localized in mast cells [138]. TNF α is stored in small amounts in the secretory granules, and its transcription is induced after mast cell activation [139]. Mast cell-derived TNF α is critical for the innate host response to bacterial peritonitis in mice via the recruitment of neutrophils [140]. Further, murine mast cells have been shown to express TLR4 for LPS [135], through which the TNF α response is elicited [141]. Increased levels of circulating TNF α are associated with cachexia. TNF α potentiates T-cell responses [107] and an antimitotic effect on fibroblasts, potentially promoting fibrosis [142,143].

TGF β is released by mouse BMMCs after IgE stimulation, and mast cell TGF β can activate embryonic dermal fibroblasts for the secretion of MCP-1 [144]. TGF β is selectively induced by IL-13, and TGF β -dependent pulmonary fibrosis is found in mice overexpressing IL-13 [145]. IL-1 β is produced by mouse mast cells on IgE stimulation [146]. In people, IL-1 is an endogenous pyrogen [147,148].

NGF is released by human and mouse mast cells in culture after IgE/antigen stimulation [149]. In a patient with SM, immunoreactive NGF was found elevated at baseline and further increases were seen after ultraviolet exposure [150]. NGF is involved in the survival and maturation of neurones and basal forebrain cholinergic nuclei [151].

SCF regulates mast cell differentiation and proliferation [152]. Human skin and lung mast cells store and secrete SCF on activation [153]. Increased interstitial SCF is found in lesional and nonlesional skin of patients with urticaria pigmentosa [154], and circulating immature mast cells in a patient with aggressive systemic mastocytosis (ASM) expressed membrane-bound SCF [9]. No increases in circulating SCF have been found in patients with SM, but a soluble form of the tyrosine kinase receptor for SCF, c-kit, is elevated in patients with indolent systemic mastocytosis (ISM), ASM, and SM-associated clonal hematologic non-mast cell lineage disease (AHNMCD) [155].

Immunomodulatory mediators

Human lung and especially intestinal mast cells release IL-4 after immune activation [156]. IL-4 is implicated in the regulation of IgE biosynthesis and in generation of the Th-2 cell phenotype [157]. For human cord blood-derived

mast cells, IL-4 has been found to regulate the expression of FcεRI, LTC₄ synthase, and cysteinyl leukotriene receptors [118,120].

IL-5 is found in mast cells in human nasal mucosa and lungs [158]. Release of IL-5 is induced by IgE/antigen activation of human mast cells [159]. IL-5 is critical to eosinophil maturation and proliferation, and antigen-sensitized mice with a disrupted IL-5 gene do not present with airway eosinophilia after aerosol challenge [160]. Elevations of serum concentrations of IL-5 can be associated with the hypereosinophilic syndrome in human beings [161,162].

IL-6 is produced by mast cells on IgE stimulation [163]. IL-6 stimulates the differentiation and maturation of B cells and the production of immunoglobulins, and IL-6 transgenic mice present with plasma cell expansion [164]. Administration of IL-6 to human patients causes an elevation in body temperature and metabolic rate [165,166].

IL-13 is produced by human lung mast cells in response to FcεRI receptor cross-linkage [145,167]. Mouse transgenic overexpression of IL-13 induces pulmonary fibrosis mediated by TGFβ [145]. Importantly, the capacity of γ-tryptase inhalation in mice to elicit airway hyperresponsiveness to methacholine is mediated by induced expression of IL-13 [168].

Chemokines

Chemokines are chemotactic cytokines regulating the migration of hematopoietic cells, including mast cells. They also promote adhesion by regulating the expression of integrins and stimulate the release of inflammatory mediators. Chemokines help to regulate angiogenesis and hematopoiesis [169,170].

Mast cell tissue localization and homing are, in part, directed by the binding of local chemokines to seven transmembrane GPCRs in their surface membrane [171,172]. Human mast cells have at least nine chemokine receptors: CXCR1, CXCR2, CXCR3, CXCR4, CX3CR1, CCR1, CCR3, CCR4, and CCR5 [173]. Binding of chemokines CXCL1, CXCL5, CXCL8, CXCL14, CX3CL1, CCL5, and CCL11 to their receptors on human mast cells has been shown to induce migration with no exocytosis or degranulation [174]. This is in contrast to basophils, which activate and degranulate in response to CCL2 and other chemokines, such as CCL3, CCL5, CCL7, and CCL8 [175]. Chemokine receptors are differentially expressed during mast cell maturation and on the different tissue mast cell phenotypes. The expression of CCR3 is predominant on MC_{Tc} in the gut, lung, and skin and increased on FcεRI-mediated activation. Because of the expression of CCR5 and CXCR4 on mast cell progenitors, they are susceptible to the M-tropic strain of HIV [176]. Once infected, mast cells become a persistent reservoir in AIDS patients [176]. Furthermore, HIV-tat protein binds to CCR3 and has been shown to be a potent chemoattractant for human mast cells. Circulating mast cell progenitors express CCR3, CXCR2, and

CXCR4, whereas tissue MCt expresses CCR1 and CCR4 and MCtc expresses CCR3, CXCR1, CXCR2, and CXCR3 [40]. Subcutaneous injection of CCL5 (Regulated on Activation Normal T-cell Expressed and Secreted) into the rat paw induces migration of mast cells in the sole, but intradermal injection into human skin results in the infiltration of eosinophils and T cells but not mast cells, consistent with the lack of CCR1 and CCR4 on human dermal mast cells [177]. GeneChip analysis of chemokine expression after FcεRI-mediated activation has identified the expression and production of multiple chemokines, such as CCL1, CCL2, CCL3, CCL4, CCL7, CCL8, CCL11 (eotaxin), CCL15 (MIP-1γ), CXCL1, CXCL2, CXCL3, CXCL5, and CXCL8. On IgE activation, CCR3, located at rest intracellularly in the secretory granules, is translocated to the surface membrane, which is then susceptible to its ligand CCL11 (eotaxin). Binding of CCL11 to CCR3 augments the FcεRI-dependent secretion of IL-13 hours after the initial activation event [178].

The role of chemokines and chemokine receptors expressed by mast cells is emerging as larger than directing homing to tissues during maturation and differentiation. The control of mast cell responses to the microenvironment during inflammation and infection and their specific tissue accumulation during allergen stimulation or in mastocytosis need further study.

Summary

Mast cells possess an array of potent inflammatory mediators capable of inducing acute symptoms after cell activation, including urticaria, angioedema, bronchoconstriction, diarrhea, vomiting, hypotension, cardiovascular collapse, and death in few minutes. In contrast, mast cells can provide an array of beneficial mediators in the setting of acute infections, cardiovascular diseases, and cancer. The balance between the detrimental and beneficial roles of mast cells is not completely understood. Although the symptoms of acute mast cell mediator release can be reversed with epinephrine, adrenergic agonists, and mediator blockers, the continued release of histamine, proteases, prostaglandins, leukotrienes, cytokines, and chemokines leads to chronic and debilitating disease, such as mastocytosis. Identification of the molecular factors and mechanisms that control the synthesis and release of mast cell mediators should benefit all patients with mast cell activation syndromes and mastocytosis.

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