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Mast cells and inflammation

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Abstract

Mast cells are well known for their role in allergic and anaphylactic reactions, as well as their involvement in acquired and innate immunity. Increasing evidence now implicates mast cells in inflammatory diseases where they are activated by non-allergic triggers, such as neuropeptides and cytokines, often exerting synergistic effects as in the case of IL-33. Mast cells can also release pro-inflammatory mediators selectively without degranulation. In particular, IL-1 induces selective release of IL-6, while corticotropin-releasing hormone secreted under stress induces the release of vascular endothelial growth factor. Many inflammatory diseases involve mast cells in cross-talk with T cells, such as atopic dermatitis, psoriasis and multiple sclerosis, which all worsen by stress. How mast cell differential responses are regulated is still unresolved. Preliminary evidence suggests that mitochondrial function and dynamics control mast cell degranulation, but not

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Disclosures

TCT is the inventor of US patents 6,635,625; 6,641,806; 6,645,482; 6,689,748; 6,984,667 and EPO 1365777 covering the role of mast cells in inflammatory diseases, US 6,020,305 covering stress-induced skin diseases, as well as US patent application 11/214,831 and 12/861,152 covering the treatment of multiple sclerosis and brain inflammation.

selective release. Recent findings also indicate that mast cells have immunomodulatory properties. Understanding selective release of mediators could explain how mast cells participate in numerous diverse biologic processes, and how they exert both immunostimulatory and immunosuppressive actions. Unraveling selective mast cell secretion could also help develop unique mast cell inhibitors with novel therapeutic applications.

Keywords

Brain; inflammation; mast cells; mitochondria; multiple sclerosis; psoriasis; skin; stress; selective release; vascular permeability

Introduction

Mast cells derive from distinct precursors in the bone marrow or other hematopoietic tissues [1,2]. They mature under the influence of local tissue microenvironmental conditions, through various cytokines such as stem cell factor (SCF) [2,3]. SCF enhances mast cell degranulation and cytokine production through cross-linking of their high affinity surface receptors for IgE (FcεRI), even though it does not induce degranulation on its own [4-7]. Other molecules that promote mast cell maturation include nerve growth factor (NGF) [8], which acts via tyrosine kinase receptors (TrkA, B, C), different from the c-kit activated by SCF [9]. Neurotrophin-3 was also shown to promote maturation of both fetal mouse skin mast cells [10] and human intestinal mast cells [11]. Moreover, human mast cells express mRNA and protein for the Trk ligands NGF, brain-derived neurotrophic factor (BDNF) and neurotrophin-3 [9], suggesting autocrine actions. However, unlike NGF, which stimulates mast cell degranulation [12], neurotrophins do not. Mast cell chemoattractants include SCF, monocyte chemoattractant protein-1 (MCP-1) and the “regulated upon activation, normal T cell expressed and secreted” (RANTES) [13]. SP is also a potent chemoattractant for human basophils [14]. Depending on their location, stage of maturation or species [15], mast cells express different types and levels of surface antigens and receptors, some of which are involved in activation and others in cell recognition (Table 1) [16].

In addition to IgE and antigen [5], immunoglobulin free light chains [17,18], anaphylatoxins, hormones and neuropeptides [19,20] can trigger mast cell secretion [21-23] (Table 2). The latter include substance (SP) [24], hemokinin [25], neurotensin (NT) [26], NGF [12,27] which is released under stress [28], and pituitary adenylate cyclase activating polypeptide (PACAP) [29,30]. Skin mast cells are located close to sensory nerve endings and can be triggered by neuropeptides [21,31], such as NT [26], NGF [12], SP [32], and PACAP [30] (Fig. 1), which can be released from dermal neurons. In fact, skin mast cells contain SP [33], while cultured mouse and human mast cells contain and secrete NGF [34]. Thymic stromal lymphopoietin (TSLP), released in response to inflammation, pathogens and trauma [35], also activates mast cells, but only in the presence of interleukin-1 (IL-1) and tumor necrosis factor (TNF) [35,36]. A number of additional immune and infectious triggers (e.g. stimulants of Toll-like receptors, TLR) can lead to *selective* release of mast cell mediators (See under “Selective release” below).

Once activated, mast cells secrete numerous vasoactive and pro-inflammatory mediators [37-42]. These include pre-formed molecules such as histamine, serotonin, TNF, kinins and proteases stored in secretory granules. Leukotrienes (LT), prostaglandins and platelet activated factor (PAF) are synthesized during mast cell activation from arachidonic acid liberated by the action of phospholipases. In addition, a number of cytokines (e.g. IL-1, 2, 5, 6, 8, 9, 13, TNF) and vascular endothelial growth factor (VEGF) [43] are synthesized *de novo* and released several hours after stimulation (Table 2). VEGF is also released from

normal human cultured mast cells selectively in response to corticotropin-releasing hormone (CRH) [44].

CRH is secreted from the hypothalamus under stress and regulates the hypothalamic-pituitary-axis (HPA) axis [45] through specific receptors [46]. These include CRHR-1 [47] and CRHR-2 [48], the latter being subdivided in CRHR-2α and CRHR-2β [49]. All CRHR are activated by urocortin (Ucn), a peptide with about 50% structural similarity to CRH [50]. Ucn II [51] and Ucn III [52] are potent selective CRHR-2 agonists. CRH can also be secreted from immune cells [53] and mast cells [54]. CRH and related peptides released locally under stress may regulate mast cell function [55], and the brain-skin connection [56]. It was recently reported that CRH stimulates generation of mast cells from human hair follicle precursors [57].

Mature mast cells vary considerably in their cytokine [58] and proteolytic enzyme content, but their phenotypic expression is not fixed [59,60]. Mast cells in the presence of SCF produce predominantly pro-inflammatory cytokines, whereas when used together with SCF and IL-4, they produce mostly Th2 cytokines [61]. For instance, human umbilical cord-derived mast cells (hCBMCs) primed with IL-4 or IL-5 before stimulation with IgE released more TNF, IL-5, and granulocyte-macrophage colony-stimulating factor (GM-CSF), compared to hCBMCs maintained in SCF alone. In contrast, IL-4 enhanced SCF-dependent mast cell proliferation and shifted IgE-stimulated response to Th2 cytokines such as IL-3, IL-5 and IL-13, but not IL-6 [62].

Mast cells play an important role in innate or acquired immunity [63], bacterial infections [64-66], as well as in autoimmunity [67]. Mast cells are also important for maturation of Th17 cells and are recognized as key cells in autoimmune disorders [68]. For instance, mast cells in the presence of IL-6 and transforming growth factor β (TGFβ) are necessary for the production of Th17 cells [69], while TNF and vasoactive intestinal peptide (VIP) drive IL-6-independent Th17 cell maturation [69-71]. A number of immune molecules also contribute to mast cell activation. Addition of complement fragment 3a (C3a) led to increased degranulation of human mast cells stimulated by aggregated IgG [72]. Immunoglobulin-free light chains elicited immediate hypersensitivity-like reactions [18,73], with subsequent T cell-mediated immune responses. The antibacterial peptides, human B-defensins, can activate mast cells and induce degranulation [74]. In fact, mast cells interact with T cells [75,76] and superactivate them through TNF, as shown with mouse [77,78] and human [79,80] mast cells. It was recently shown that T cells release “microparticles” that stimulate human mast cell degranulation and IL-8 release [81]. Mast cells, in turn, secrete heparin “microparticles” that contain and deliver TNF to lymph nodes [82].

Mast cells, specifically a subset highly expressing both FcεRI and MHC II [83], can function as antigen presenting cells [84-86]. Basophils can also act as Th2-inducing antigen-presenting cells [87,88]. Basophils promote Th2 responses [89,90] and co-operate with dendritic cells for optimal Th2 responses [91]. Moreover, basophil activation by “autoreactive IgE” induces their “homing” to lymph nodes, where they promote Th2 cell differentiation and production of auto-reactive antibodies that contribute to lupus nephritis [92]. Interestingly, mast cells can act both as positive and negative modulators of immunity [93]. In addition, mast cells can coordinate the adaptive immune response by directing migration of dendritic and T cells to lymph nodes and secreting T cell-polarizing cytokines [94]. Such regulatory activities of mast cells may stem from *selective* release of immunomodulatory molecules that could have both autocrine and paracrine actions (Fig. 2).

Mast cells also have the unusual ability to be triggered by certain molecules and then either activate them or degrade them. For instance, mast cells can act on precursor protein

molecules and generate active peptides [95], such as histamine-releasing peptides [96] and NT, [97] from plasma. However, mast cells can also degrade NT [98] and limit its biologic effects [99]. Mast cells can also synthesize endothelin [100], but also release proteases that degrade endothelin [64]. Finally, mast cells can be activated by snake toxins [101,102], but also degrade them [103]. Whether these actions will prove useful or detrimental obviously depends on the ability of mast cells to secrete specific mediators selectively in a well-regulated fashion.

Inflammatory processes and the role of selective release

Increasing evidence indicates that mast cells are critical for the pathogenesis of inflammatory diseases [19,20], such as arthritis [104], atopic dermatitis, psoriasis [105,106], and multiple sclerosis [107] (Fig. 3). Gene array analysis of human mast cells activated by IgE showed overexpression of numerous, mostly inflammation-related genes [108]. Proteases released from mast cells could act on plasma albumin to generate histamine-releasing peptides [96,109] that would further propagate mast cell activation and inflammation. Proteases could also stimulate protease-activated receptors (PAR) inducing microleakage and widespread inflammation [110,111]. However, unlike allergic reactions, mast cells are rarely seen to degranulate during inflammatory processes. The only way to explain mast cell involvement in non-allergic processes would be through *"differential"* or *"selective"* secretion of mediators without degranulation [112].

This ability could occur through different mechanisms: (A) mast cells can secrete the content of individual granules [113]; (B) mast cells can secrete some granular contents through a process associated with ultrastructural alterations of their electron dense granular core indicative of secretion, but without evidence of degranulation [114], a process that has been termed "activation" [115], "intragranular activation" [116] or "piecemeal" degranulation [117] (Table 3, Fig. 4); (C) mast cells can undergo selective release of specific mediators such as serotonin without histamine [118]. Selective release of serotonin occured through sequestration from secretory granules inside vesicles containing high affinity serotonin-binding proteins from which it was released [119]. A somewhat similar process was reported for eosinophils where it was shown that eotaxin stimulation induced movement of preformed IL-4 from granules into secretory vesicles from which it was released [120]. Human mast cells stimulated by IL-1 selectively released IL-6 without degranulation through vesicles (40-80 nm) much smaller than the secretory granules (800-1000 nm) [121]. Selective release of eicosanoids has also been shown [122-124].

Selective release of IL-6 was reported in response to bacterial lipopolysaccharide (LPS), in the presence of the phosphatidylinositol 3-kinase (PI3-K) inhibitor wortmannin, or triggered by SCF [125-127]. CRH induced selective VEGF release [128], and PGE_2 also induced release of VEGF [129] and MCP-1 without degranulation [130]. Yet, PGE_2 *inhibited* FcεRI-induced histamine release from human lung mast cells [131]. Stromal cell-derived factor-1 alpha (SF-1α) selectively produced IL-8 from human mast cells without degranulation as well [132]. Activation of human cultured mast cells by CD30 ligands led to release of the chemokines IL-8 and MCP-1 without histamine and without degranulation [133]. IL-33 induced IL-13 release independent of IgE stimulation [134].

TLR are critical in innate and acquired immunity [135,136]. TLR activation on mast cells leads to release of different cytokines [137]. For instance, rodent mast cell TLR-4 activation by LPS induces TNF release without degranulation. TLR-4 is also activated by extra domain A of fibronectin to release several cytokines, including TNF, in the same way as LPS [138]. Furthermore, LPS induces secretion of IL-5, IL-10 and IL-13, but not GM-CSF, IL-1 or LTC_4. [139,140]. In contrast, staphylococcal peptidoglycan induces degranulation and

histamine release through TLR-2 [139,141]. TLR-2 and TLR-4 activation has a synergistic action with antigen in enhancing cytokine production from rodent mast cells [142]. Elsewhere, it was shown that TLR-2 activation produces IL-4, IL-6 and IL-13, but not IL-1, while LPS produces TNF, IL-1, IL-6 and IL-13, but not IL-4 or IL-5, again without degranulation [143].

TLR 3, 7 & 9 activation by poly-oligodeoxynucleotide and CpG induces release of TNF and IL-6 without degranulation from fetal rat skin-derived mast cells [144]. Human mast cells produce IL-6 through viral TLR-9 activation [145], while they produce interferon (IFN) following TLR-3 activation by double-stranded RNA [146].

Regulation of mast cell activation

FcεRI-induced mast cell degranulation involves calcium-dependent exocytosis, and SNAP-23 phosphorylation [147], but granule translocation to the surface is calcium-independent [148]. Mast cell activation by different triggers apparently engages different downstream pathways. FcεRI aggregation induces PI3K, ERK, JNK, NF-κB and PKC activation, although the PKCε isozyme may be redundant [149,150]. PI3K inhibition by the "phosphatase and tensin homologue deleted on chromosome ten" (PTEN) or PTEN knockdowns induce constitutive cytokine production, without degranulation, that involves phosphorylation of AKT, p38/MAPK and JNK [151]. Secretion in response to compound 48/80 requires PLC, tyrosine kinase, p38/MAPK and PKC [152]. In contrast, IL-1 stimulation of selective IL-6 release is extracellular calcium-independent and involves p38/MAPK, but only PKCθ isozyme activation [153]. CRH-induced selective VEGF release from mast cells is also extracellular calcium-independent, and involves only PKA and p38/MAPK activation [128].

Degranulation in response to FcεRI-aggregation was severely impaired in IL-2-inducible T cell kinase −/− mice [154]. FcεRI-induced mast cell activation in rat basophil leukemia (RBL) cells was inhibited by the Syk-tyrosine kinase inhibitor Piceatannol [155]. Suboptimal antigen challenge of human mast cells led to FcεRI-unresponsiveness that correlated with reduced Syk levels [156], apparently through actin assembly that blocked degranulation [157]. However, low antigen still permitted MCP-1 release, suggesting yet another mechanism of differential release [158].

The Src family kinase Lyn is a negative regulator of allergic mast cell activation, but Lyn −/− mice had increased FcεRI expression, circulating histamine and eosinophilia [159]. Fyn deficient mast cells could not generate IL-6, TNF or MCP-1 during FcεRI aggregation, but IL-13 production was intact, suggesting divergent regulatory pathways [160].

Adaptor complexes such as B cell lymphoma 10-mucosal-associated lymphoid tissue 1 (Bcl10-Malt1) permit FcεRI-dependent IL-6 and TNF release without degranulation [161]. Mice deficient in either Bcl10 or MALT1 proteins did not produce TNF or IL-6 upon FcεRI signaling: yet, degranulation and LT secretion was normal [162]. Neutralization of the inhibitory receptor IRp60 (CD300a) in human cord blood mast cells in mice led to increased mediator release [163]. In contrast, engagement of the myeloid cell inhibitory receptor CD200 in human mast cells inhibited FcεRI-induced activation [164]. Mast cells also express the inhibitory receptors CD300 and Siglec-8, as well as the death receptor TRAIL [165]. Two peptides derived from the complement components C3a, C3a+ and C3a9 inhibited FcεRI-induced degranulation and TNF release [166].

There appear to be some innate inhibitors of mast cell secretion (Fig 2). Chondroitin sulfate and heparin, the major constituents of mast cell granules, inhibit human mast cell secretion [167]. Nitric oxide (NO) blocks FcεRI-induced cytokine secretion through inhibition of Jun

[168]. In contrast IL-10 appears to have divergent effects depending on the mast cell type and stimulus [169]. The natural chymase inhibitors alpha 1-antitrypsin and secretory leukocyte protease inhibitor (SLPI) inhibit histamine release from human cells [170].

Recent evidence indicates that mitochondria are involved in the regulation of mast cell degranulation (Fig. 4). Mitochondrial uncoupling protein 2 (UCP2) inhibited mast cell activation [171]. Moreover, our recent results indicate that mast cell degranulation requires mitochondrial translocation to the cell surface [172] (Fig. 5). Inhibition or downregulation of Dynamin Related Protein 1 (Drp1), a cytoplasmic protein responsible for mitochondrial fission and translocation, blocks mast cell degranulation [173]. The involvement of mitochondria in mast cell regulation may also explain the ability of certain flavonoids [174] to inhibit mast cell degranulation [175], since quercetin was shown to accumulate in mitochondria [176].

Atopic dermatitis and psoriasis

Skin mast cells may have important functions as “sensors” of environmental and emotional stress [56], possibly due to direct activation by CRH secreted under stress, and related peptides [55]. Mast cell-related atopic dermatitis (AD) and psoriasis, are triggered or exacerbated by stress through mast cell activation [177,178]. Mast cell activation in AD may also be induced by cytokines, such as TSLP. We recently reported increased serum levels and skin gene expression of TSLP in AD patients as compared to controls [179], in agreement with previous studies [180,181].

Computer-induced stress enhanced allergen specific responses with concomitant increase in plasma SP levels in patients with AD [182]. Similar findings with increased plasma levels of SP, VIP and NGF, along with a switch to a Th2 cytokine pattern, was reported in patients with AD playing video games [183]. Skin has its own equivalent of the HPA axis [184,185]. CRH and CRHR mRNA is expressed in human and rodent skin [186,187] and CRH can be secreted from dorsal root ganglia and from sympathetic ganglia [188,189]. CRH administration in humans causes peripheral vasodilation and flushing reminiscent of mast cell activation [190]. Moreover, intradermal administration of CRH and Ucn activates skin mast cells and increases vascular permeability in rodents [191] and humans [192,193], through activation of CRHR-1 [56]. CRHR-1 expression was increased in chronic urticaria [194]. Acute stress released CRH in the skin and increased local vascular permeability [195]. Acute stress also exacerbated skin delayed hypersensitivity reactions [196], and chronic contact dermatitis in rats, an effect that involved significantly increased mast cells in the dermis, and was dependent on CRHR-1 [197]. Acute restraint stress induced rat skin vascular permeability [198], which was inhibited by a CRH receptor antagonist, and was absent in mast cell deficient mice [191,199].

Psoriasis is also triggered or exacerbated by acute stress [105,200-202]. We showed that psoriasis is associated with increased serum CRH and decreased lesional skin CRHR-1 gene expression possibly due to downregulation [203]. Psoriasis is characterized by keratinocyte proliferation and inflammation, as well as mast cell accumulation and activation [106,204]. Mast cells are increased in lesional psoriatic skin [105,106]. Neuropeptides [205], especially SP [206], are involved in the pathogenesis of psoriasis. In particular, SP reactive fibers are localized close to mast cells [105,207]. SP can stimulate mast cells [208,209] and contributes to inflammation [210,211]. SP-positive nerve fibers are more dense in psoriatic lesions and have an increased number of mast cell contacts compared to normal skin [207,212,213]. SP-positive nerve fibers and mast cell contacts are also increased by acute stress in mice [214], leading to dermal mast cell degranulation [201,208,215]. Keratinocytes also express neurokinin (NK) 2 receptors and can be stimulated by SP [216], to release IL-1

[217]. Keratinocyte proliferation is accelerated by PAF, which can be secreted from mast cells [218], and stimulates human mast cells [219].

Psoriasis is associated with chronic inflammation and it often co-exists with inflammatory arthritis [220], in which IL-33 was recently implicated [221]. IL-33 is one of the newest members of the IL-1 family of inflammatory cytokines [222], and can mediate IgE-induced anaphylaxis in mice [223]. IL-33 also induces release of IL-6 from mouse bone marrow-derived cultured mast cells [224], and IL-8 from hCBMCs [225]. We showed that IL-33 augments SP-stimulated VEGF release from human mast cells and IL-33 gene expression is increased in lesional skin from patients with psoriasis [226]. Mast cells may, therefore, be involved in the pathogenesis of psoriasis and other inflammatory skin diseases.

Multiple sclerosis

Functional mast cell-neuron interactions occur in the brain [227,228] and could mediate neuroinflammation [20]. In the brain, mast cells are found in the leptomeninges [228,229], the choroid plexus, thalamus and hypothalamus, especially the median eminence [230,231], where most of histamine derives from mast cells [232-235]. We had proposed that mast cells can act as *"the immune gate to the brain"* [107], and we later showed that mast cells regulate BBB permeability [236,237]. BBB breakdown [238] precedes any pathological or clinical signs of MS [239-241], as shown by MRI-gadolinium studies and trans-BBB leakage of albumin [242]. Mast cells have been implicated in multiple sclerosis (MS), a demyelinating condition involving brain and MS plaque infiltration [243] by lymphocytes and activated mast cells [244,245]. Gene array analysis of MS plaques showed overexpression of genes for FcεRI, the histamine-1 (H_1) receptor and tryptase, all of which are associated with mast cells [246,247]. A recent paper reported that experimental allergic encephalomyelitis (EAE) development depends on H_1 receptor activation [248]. Mast cells are located close to the cerebral microvasculature and do not express FcεRI protein under normal conditions [249]. This is not surprising as the brain is not known to develop allergic reactions since IgE does not cross the blood-brain-barrier (BBB). Brain mast cells also do not normally express their surface growth factor (c-kit) receptor [250], but do so during EAE [251]. We first showed that mast cells migrate into the brain from the meninges, and it was later shown that they can also enter the CNS from blood [252]. Mast cell-derived products can enter neurons, a process termed "transgranulation", indicating a novel form of brain-immune system communication [253]. We further hypothesized that perivascular brain mast cells could come in contact with circulating T cells and not only allow them to enter the BBB, but also activate them [80]. TNF can be released from rat brain mast cells [254], and is involved in both brain inflammation [255,256] and increased vascular permeability [257]. Mast cell tryptase is elevated in the CSF of MS patients [258] and can activate peripheral mononuclear cells to secrete TNF and IL-6 [259], as well as stimulate PAR that can lead to microvascular leakage and widespread inflammation [260]. It was recently reported that meningeal mast cells promote T cell infiltration in the CNS by disrupting BBB integrity through TNF [261]. However, this paper did not include any of earlier publications discussed above and did not consider the possibility that lack of TNF may eventually worsen EAE [262]. The above findings imply that mast cells may be able to secrete both prestored and de novo synthesized TNF [263,264] with different biological actions.

The role of $CD4^+$ T cells is well-documented in MS, but this CD4-Th1 model has recently been questioned [265], because increasing evidence also implicates Th2 processes typically associated with allergic reactions [266,267]. Some studies reported the inability of mast cell deficient mice to fully develop EAE, but suggested that reduced T cell activation may also be involved [268,269]. Mast cell contact with activated T cells leads to secretion of matrix metalloproteinase (MMP)-9 and IL-6 from human mast cells [270]. Moreover, mast cells

can promote IgE-dependent and T cell-independent proliferation and activation through TNF release [77], [78]. We showed that mast cells superstimulate activated T cells, an action which is further increased when mast cells are activated by myelin basic protein (MBP) and is partially dependent on TNF [79,80]. MBP could induce homogeneic mast cell activation and brain demyelination [271]. Moreover, virally-induced encephalomyelitis could not develop in W/W^v mast cell deficient mice, and EAE was attenuated and delayed in these mice [272].

Mast cell-derived mediators can increase BBB permeability [273]. Selective release of IL-6 could have profound effects on brain function [274] and could activate the HPA axis [275]. Selective release of VEGF, an isoform of which is particularly vasodilatory [43,276], could lead to BBB disruption [277]. Mast cells are localized close to CRH-positive neurons in the median eminence [278] and express functional CRH receptors [44]. Activation of hypothalamic mast cells can stimulate the HPA axis [279-281], through histamine, which regulates the hypothalamus, and can also increase hypothalamic CRH mRNA expression [282]. Moreover, human mast cells can synthesize and secrete large amounts of CRH [283], as well as IL-1 and IL-6 which are independent activators of the HPA axis [284].

The effect of stress and CRH on mast cell activation and BBB permeability may help explain some of the clinical findings in MS patients. Acute stress worsens the symptoms of MS, and the appearance of new MRI lesions has been repeatedly shown to be precipitated by psychological stress [285-288]. In one study in Denmark, parents who had unexpectedly lost a young child had a significantly increased risk of MS, compared to other bereaved parents [289]. Meta-analysis of 14 prospective studies showed a significantly increased risk of MS exacerbations after stressful events [290]. A review of the effect of stress on MS proposed that it may be due to glucocorticoid-insensitive immune cells [291]. Another study argued that stress could not affect MS because the function of peripheral blood leukocytes in MS patients was apparently unaffected by stress [292]. However, such findings may not be relevant as stress may predominantly affect mast cells and T cells, but not peripheral leukocytes. Release of CRH and cytokines outside the brain may be more relevant instead. For instance, examination-stress dramatically increased serum TNF levels in medical student volunteers [293], and restraint stress induced mast cell-dependent increase in mouse serum IL-6 [294]. Rat brain mast cells were activated by acute stress, and led to CSF elevation of rat mast cell protease I [278], the equivalent of tryptase in humans. These effects were abolished by polyclonal antiserum to CRH and by the CRHR-1 antagonist Antalarmin [228,278]. A short period of restraint [295] or maternal deprivation stress [296] increased the severity of EAE. Acute restraint stress also shortened the time required for the development of EAE in mice [295]. Moreover, EAE was characterized by decreased clinical disability and brain infiltration by immune cells in CRH −/− mice as compared to normal controls [297]. Restraint stress was also reported to increase mortality rates and lead to higher CNS viral load during Theiler's virus infection [298]. Stressed mice had increased inflammatory spinal cord lesions and developed autoimmune antibodies to MBP [299]. Mast cell activation was shown to occur in response to isolation stress [300], restraint stress [278], subordination stress [301], and during courtship following isolation of male doves [302].

Mast cells could, therefore, participate in the pathogenesis of MS in many different ways: they could (A) be stimulated to release cytokines/chemokines selectively inducing T cell/macrophage recruitment and activation; (B) present myelin antigens to T cells; (C) disrupt the BBB and permit entry of active T cells that are sensitized to MBP; (D) damage myelin and release fragments that could stimulate secretion of tryptase, which may in turn enhance demyelination and induce further inflammation through stimulation of PAR. As a result mast cells were considered as a possible therapeutic target for MS [303]. It is of interest that flavonoids [174] known to inhibit mast cell secretion [175] have also been shown to inhibit

macrophage myelin phagocytosis [304], and EAE [305,306]. The flavone luteolin, which is structurally related to quercetin, was also a strong inhibitor of human autoimmune T cells [307]. Quercetin and luteolin also inhibit IL-6 release from microglia [308] and induce an anti-inflammatory phenotype [309]. Luteolin is neuroprotective [309] and is closely related to dihydroxyflavone recently shown to mimic the action of BDNF [310]. We showed that luteolin can inhibit mast cell activation and mast cell-dependent superstimulation of activated T cells with or without stimulation by MBP [80]. Luteolin can also inhibit activation of peripheral lymphocytes from MS patients [311], and it was, therefore, proposed as adjuvant therapy for MS [312].

Conclusion

Mast cells clearly participate in the induction and/or propagation of certain inflammatory diseases, through selective release of mediators. The pharmacologic inhibition of this process would, therefore, have clear therapeutic potential. Luteolin formulations, alone or together with drugs that can selectively inhibit the release of pro-inflammatory mediators hold promise for the treatment of skin and brain inflammatory diseases.

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Abbreviations

AD	atopic dermatitis
BBB	blood-brain barrier
Bcl10-Malt1	B cell lymphoma 10-mucosal-associated lymphoid tissue 1
BDNF	brain-derived neurotrophic factor
CRH	corticotropin-releasing hormone
CRHR	corticotropin-releasing hormone receptor
Drp1	dynamin related protein 1
EAE	experimental allergic encephalomyelitis
FcεRI	high affinity surface receptors for IgE
GM-CSF	granulocyte-macrophage colony-stimulating factor
hCBMCs	human umbilical cord-derived mast cells
HPA	hypothalamic-pituitary-adrenal
IFN	interferon
IL	interleukin
LPS	lipopolysaccharide
LT	leukotriene
MBP	myelin basic protein
MCP-1	monocyte chemoattractant protein-1

MS	multiple sclerosis
MMP	matrix metalloproteinase
NGF	nerve-growth factor
NK	neurokinin
NT	neurotensin
PACAP	pituitary adenylate cyclase activating polypeptide
PAF	platelet activating factors
PAR	protease activated receptors
PI3-K	phosphatidylinositol 3-kinase
PTEN	phosphatase and tensin homologue deleted on chromosome ten
RANTES	regulated upon activation normal T cell expressed and secreted
RBL	rat basophil leukemia
SCF	stem cell factor
SF-1α	stromal cell-derived factor-1 alpha
SLPI	secretory leukocyte protease inhibitor
SP	substance P
TGFβ	transforming growth factor β
TLR	toll-like receptors
TNF	tumor necrosis factor
TSLP	thymic stromal lymphopoietin
Ucn	urocortin
UCP2	uncoupling protein 2
VEGF	vascular endothelial growth factor
VIP	vasoactive intestinal peptide.

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Research highlights

- Mast cells release pro-inflammatory mediators selectively without degranulation
- Mast cells are activated by CRH released under stress
- Neuropeptide mast cell triggers have synergistic action with cytokines, like IL-33
- Unique flavonoid combinations can effectively block mast cell secretion
- Mast cells may serve as new therapeutic targets for psoriasis and multiple sclerosis

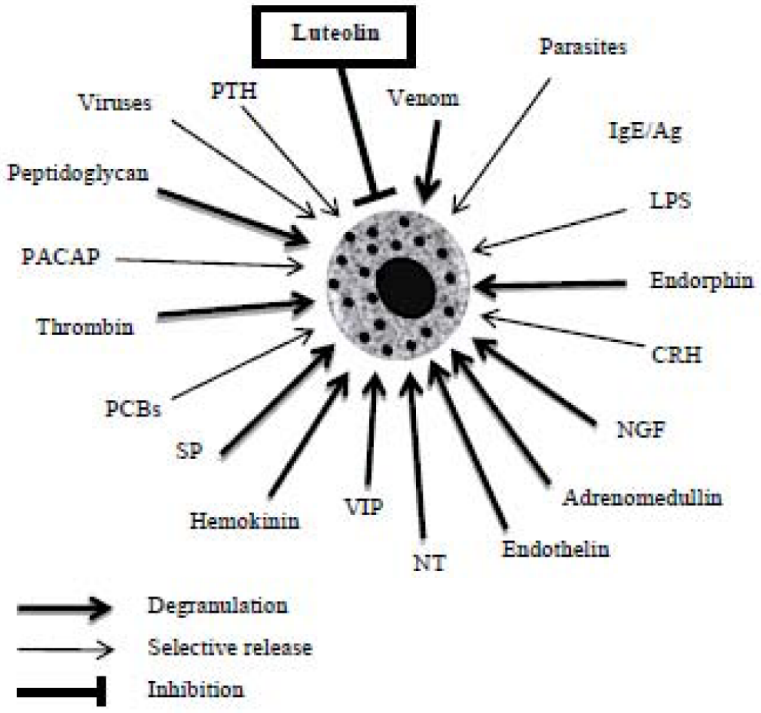

Figure 1.

Schematic representation of physiological and environmental mast cell triggers, and the inhibitory effect of certain flavonoids, such as luteolin. Many of these triggers stimulate selective release of mediators such as IL-6, TNF or VEGF without degranulation.

CRH, corticotropin releasing hormone; LPS, lipopolysaccharide; NT, neurotensin; PACAP, pituitary adenylate cyclase activating polypeptide**;** PCBs, polychlorinated biphenols; PTH, parathyroid hormone; SP, substance P; VIP, vasoactive intestinal peptide.

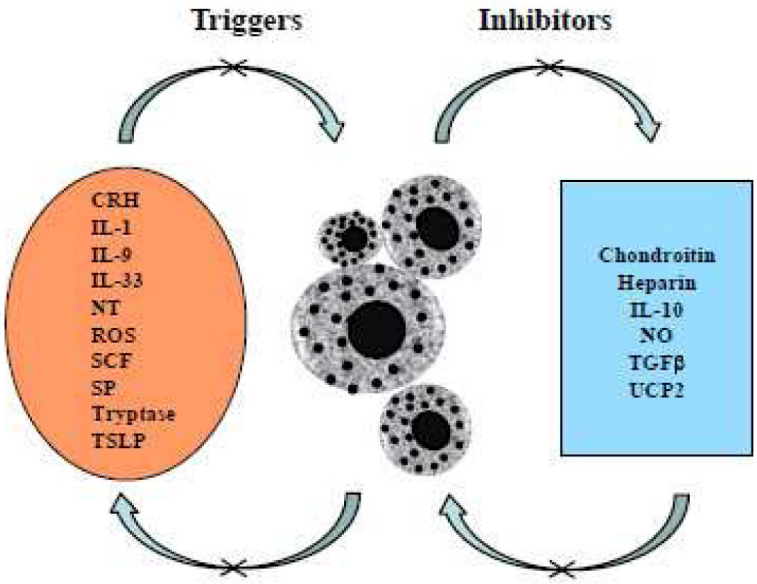

Figure 2.

Schematic representation of mast cell autocrine triggers and modulators. Numerous molecules secreted by mast cells can have autocrine actions, either activating or inhibiting mast cells.

CRH, corticotropin-releasing hormone; IL, interleukin; NT, neurotensin; NO, nitic oxide; ROS, reactive oxygen species; SCF, stem cell factor; SP, substance P; TGFβ, transforming growth factor β; TSLP, thymic stromal lymphopoietin; UCP2, uncoupling protein 2.

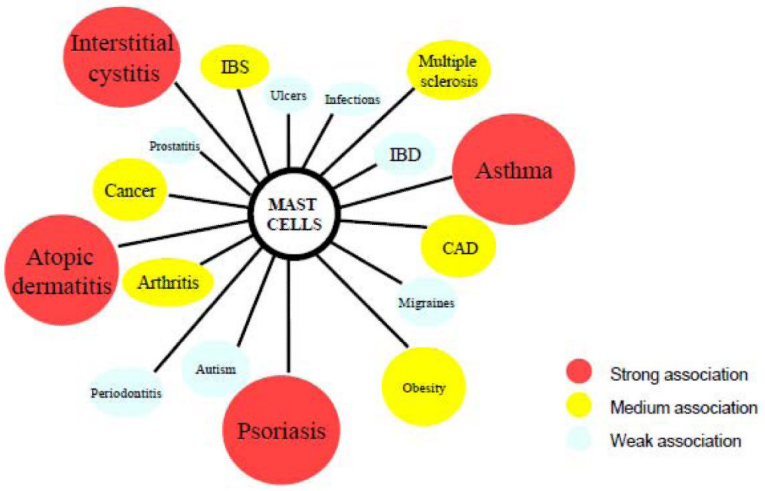

Figure 3.

Mast cell involvement in inflammatory diseases. Increasing evidence indicates that mast cells are involved in many diseases. Colors indicate the strength of the association (red = strongest, white = weakest).

CAD, coronary artery disease; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome.

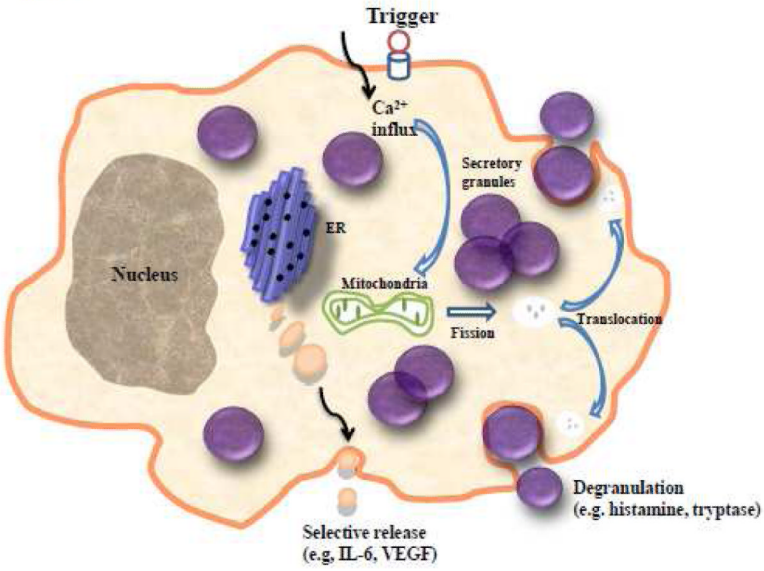

Figure 4.

Schematic representation showing mast cell degranulation as compared to selective mediator release. During selective release, vesicles much smaller than secretory granules transport mediators to the cell surface for exocytosis.

ER, endoplasmic reticulum; VEGF, vascular endothelial growth factor.

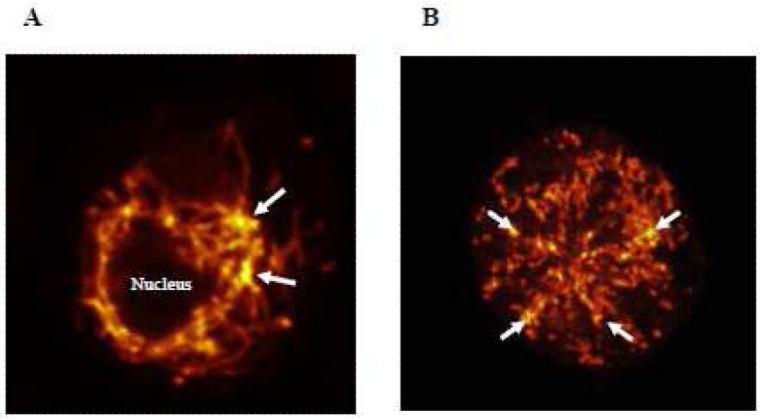

Figure 5.
Two human cultured LAD2 mast cells, showing distribution of mitochondria stained with MitoTracker and photographed using Confocal microscopy; (A) control in which mitochondria form a “net” around the nucleus and (B) after stimulation with SP (2 M for 30 min at 37°C) in which mitochondria are distributed throughout the cell. (Magnification: x 1000). Arrows point to the areas with the highest concentration of MitoTracker (yellow color); thus the highest aggregation of mitochondria.

Table 1

Mast cell receptors and their agonists*

Adenosine receptors **A2A, A2B, A3**	**Adenosine**
β2-Adrenoreceptor	Adrenaline
C3αreceptor	C3α
C5α receptor	C5α
Cannabinoid CB_2 receptor	2-Arachidonoyl-glycerol, anandamide
CD47 (=integrin-associated protein, IAP)	Integrins
CD200 receptor	CD200 (0X2)
$Cd300_{\alpha}$ receptor	Eosinophil granule proteins
Chemokine receptors CXCR1-4, CX3 CR1, CCR1,3-5	Chemokines
CRHR-1, CRHR-2	Corticotropin releasing hormone
Estrogen receptors (A,B)	Estrogens
FcαR (CD89)	IgA
FcεRI	IgE
FcγRI	IgG
FcγRIIA	IgG
FcγRIIB	IgG
FcγRIII	IgG
GPR34	Lysophosphatidylserine
GPR92	Lysophosphatidic acid
Histamine receptors H_1, H_2, H_3, H_4	Histamine
$5\text{-}HT_{1A}$	Serotonin
Kit receptor tyrosine kinase (CD17)	Stem cell factor
LPA_1, LPA_3	Lysophosphatidic acid
Leptin receptor	Leptin
Leukotriene receptors 1 and 2	Leukotrienes
MRGX2	Mastoparan, somatostatin, SP
Myeloid-associated Ig-like receptor 1	?
Neurokinin receptors NK1R, NK2R, NK3R, VPAC2	CGRP, Hemokinin-A, SP, VIP
Neurotensin receptor	Neurotensin
Neurotrophin receptors TrkA TrkB TrkC	 NGF BDNF Neurotrophin 3
Nicotinic acetylcholine receptor	Acetylcholine
0X40	0X40-ligand
Protease activated receptors 1-4	Serine proteases (e.g. trypsin, tryptase)
Peripheral benzodiazepine receptor	?

Adenosine receptors **A2A, A2B, A3**	**Adenosine**
Progesterone receptor	Progesterone
Prostaglandin E receptors EP_2, EP_3, EP_4	Prostaglandin E
Purinoreceptors P2Y1, P2Y12, P2Y13, P2Y2, P2Y11	 ADP ATP, UTP ATP
Sphingosine-1-phosphate $S1P_1$, $S1P_2$, $S1P_5$	S1P
Toll-like receptors 1-9	Bacterial and viral products
Urokinase receptor	Urokina5s2e
Vitamin D receptor	Vitamin D

* There are differences in the expression of cell surface receptors between human and rodent mast cells.

Table 2

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(CXCL8), MCP-1(CCL2), MCP-3(CCL7), MCP-4, RANTES (CCL5), Eotaxin (CCL11)	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
Matrix metalloproteinases	Tissue damage, modification of cytokines/chemokines
Peptides	
Angiogenin	Neovascularization
Corticotropin-releasing hormone	Inflammation, vasodilation
Endorphins	Analgesia
Endothelin	Sepsis
Kinins (bradykinin)	Inflammation, pain, vasodilation
Leptin	Food intake regulator
Renin	Angiotensin synthesis
Somatostatin	Anti-inflammatory (?)
Substance P	Inflammation, pain
Urocortin	Inflammation, vasodilation
VEGF	Neovascularization, vasodilation
Vasoactive intestinal peptide	Vasodilation, mast cell activation
Proteoglycans	
Chondroitin sulfate	Cartilage synthesis, anti-inflammatory
Heparin	Angiogenesis, nerve growth factor stabilization
Hyaluronic acid	Connective tissue, nerve growth factor stabilization
De novo synthesized	
Cytokines	
Interleukins (IL)-1,2,3,4,5,6,8,9,10,13,16,18	Inflammation, leukocyte migration, pain
IFN- α , IFN-β, IFN-γ; MIF; TGFβ; TNF-α, MIP-1α, MCP-1	Inflammation, leukocyte proliferation/activation
Growth Factors	
SCF, GM-CSF, β-FGF, neurotrophin 3, NGF,	Growth of a variety of cells

Mediators	Main Pathophysiologic Effects
PDGF, TGFβ, VEGF	
Nitric oxide	Vasodilation
Phospholipid metabolites Leukotriene B_4	Leukocyte chemotaxis
Leukotriene C_4	Vasoconstriction, pain
Platelet activating factor	Platelet activation, vasodilation
Prostaglandin D_2	Bronchonstriction, pain

β-FGF, β-fibroblast growth factor; GM-CSF, granulocyte monocyte-colony stimulating factor; IFNγ, interferon-γ; MCP, monocyte chemoattractant protein; MIF, macrophage inflammatory factor; MIP, macrophage inflammatory protein; NGF, nerve growth factor; PDGF, platelet-derived growth factor; SCF, stem cell factor; TGFβ, transforming growth factor β ; TNF-α, tumor necrosis factor-α; VEGF, vascular endothelial growth factor.

* There are differences in the expression of mediators between human and rodent mast cells.

Table 3

Selective release of mast cell mediators

Stimuli	MC type	Mediators released	Mediators NOT released	Pathophysiological importance	References
ENDOGENOUS					
CD8 ligands	RPMC	TNF, NO	H	T cell interaction	[279]
CRH	hCBMC	VEGF	H, tryptase, IL-8	Inflammation	[25]
Endothelin-1 -3	RMMC	TNF, IL-12↑	IL-4, IL-10, IL-134*	Th1 immunity	[280]
IL-1	hCBMC	IL-6, IL-8, TNF	H, tryptase	Inflammation	[92]
IL-1β	RPMC	NO	PAF, H	Inflammation	[281]
IL-12	P815	IL-13		Host defence against bacteria	[282]
IL-12	RPMC	IFN-y	H	Th1 immunity	[283]
LTC_4/LTD_4	IL-4-primed hCBMC	TNF, MIP-1α, IL-5	H	Non-IgE mediated inflammation	[284]
Monomeric IgE	BMMC	IL-6	H, LTC_4	Mast cell survival	[285]
PGE_2	RPMC	IL-6	H, TNF	Cytoprotection	[286]
SCF	BMMC	IL-6	H, LTC_4, TNF	Mast cell development	[83]
SDF	hCBMC	IL-8	H, GM-CSF, IFN-γ, IL-1β	Endothelial transmigration	[88]
Thrombin	BMMC	IL-6	Serotonin, TNF	Anticlotting	[287]
Urocortin	hCBMC	IL-6	H, tryptase, IL-8, VEGF	Inflammation	[288]
EXOGENOUS/PHARMACOLOGICAL					
Amitriptyline	RPMC	Serotonin	HA	Headaches	[73]
Cholera Toxin	RPMC	IL-6	HA, TNF	Inflammation	[289]
Clostridium difficile Toxin A	RPMC	TNF	HA	GI tract inflammation	[290]
CpG DNA	BMMC	TNF, IL-6	HA, IL-4, IL-12, GM-CSF, IFN	Host response to bacteria	[291]
H. pylori VacA Toxin	BMMC	IL-6, IL-8, TNF	HA	Gastric injury	[102]
LPS (TLR-4)	RPMC	IL-6	HA	Bacterial infection	[81]
PMA	BMMC	VPF/VEGF	5HT	Angiogenesis	[292]

Stimuli	MC type	Mediators released	Mediators NOT released	Pathophysiological importance	References
S.a.peptidoglycan (TLR-2)	hCBMC	HA, IL-1p, RANTES, LTC_4	IL-6	Exacerbation of asthma by bact. infection	[98]
Suboptimal FcεRI stimulation	BMMC	MCP-1, HA low	IL-10, HA	Chemokines ⩽Cytokines /HA	[120]
Viruses (TLR-3,5,9)	FSMC	TNF, IL-6	HA	Recruitment of other immune cells	[103]

BMMC, bone marrow mast cells; CRH, corticotropin-releasing hormone; FSMC, fetal skin-derived cultured mast cells; GM-CSF, granulocyte monocyte-colony stimulating factor; H, histamine; HA, hexosaminidase; hCBMC, human cord blood-derived mast cells; IFN, interferon; LT, leukotriene; MCP, monocyte chemoattractant protein; MIP, macrophage inflammatory protein; NO, nitric oxide; PAF, platelet activating factor; PMA, phorbol myristate acetate; PG, prostaglandin; RMMC, rat mucosal mast cells ; RPMC, rat peritoneal mast cells; SCF, stem cell factor; SDF, stromal cell-derived factor; TLR, toll-like receptor; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor