Mast Cells in Allergic and Inflammatory Diseases

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Abstract: Mast cells are important in the development of allergic and anaphylactic reactions, but also in acquired and innate immunity. There is also increasing evidence that mast cells participate in inflammatory diseases, where they can be activated by non-allergic triggers, such as neuropeptides and cytokines, often having synergistic effects as in the case of substance P (SP) and IL-33. Secretion of vasoactive mediators, cytokines and proteinases contribute to the development of coronary artery disease (CAD), as well as to diet-induced obesity and the metabolic syndrome. Mast cells may be able to orchestrate such different biological processes through their ability to release pro-inflammatory mediators selectively without the degranulation typical of allergic reactions. Recent evidence suggests that mitochondrial uncoupling protein 2 (UCP2) and mitochondrial translocation regulate mast cell degranulation, but not selective mediator release. Better understanding of these two processes and how mast cells exert both immunostimulatory and immunosuppressive actions could lead to the development of inhibitors of release of specific mediators with novel therapeutic applications.

Keywords: Coronary artery disease, diabetes, inflammation, mast cells, mitochondria secretion.

INTRODUCTION

In addition to allergic and anaphylactic reactions [1-3], mast cells are now considered to play an important role in a wide spectrum of biological reactions ranging from innate and acquired immunity [4,5], to autoimmunity [4], inflammation [2,6], antigen presentation [7,8], bacterial infections [9-11], tissue repair [12], angiogenesis [13-16], cancer [17], as well as coronary plaque formation and metabolic syndrome [18-20]. Interestingly, mast cells can act as both positive and negative modulators of immunity [21].

Mast cells derive from distinct precursors in the bone marrow [22,23] or other hematopoietic tissues [24]. They undergo maturation in various tissues under the influence of local microenvironmental factors, such as stem cell factor (SCF) acting on the tyrosine kinase-activated receptor c-kit [23,25], which also enhances cytokine production through cross-linking of the high affinity surface receptors for IgE (FcεRI) [26-29]. Depending on the stage of maturation, location, or different species [30], mast cells express different types and levels of surface antigens and receptors, some of which are involved in activation and others in cell recognition [2,31]. Other molecules that promote mast cell maturation include nerve growth factor (NGF) [32], which acts via tyrosine kinase receptors (TrkA, B, C), different from the c-kit [33]. Neurotrophin-3 also promotes maturation of both fetal mouse skin mast cells [34] and human intestinal mast cells [35]. In addition, human mast cells express mRNA and protein for the Trk ligands neurotrophin-3, NGF, and brain-derived neurotrophic factor (BDNF) [33], suggesting autocrine actions. However, neurotrophins, unlike NGF, do not stimulate mast cell degranulation [36]. It was recently reported that corticotropin-releasing hormone (CRH), produced locally in the skin [37] stimulates human hair follicle precursors to develop into mast cells [38] through CRH receptors [39]. CRH can also be secreted from immune cells [40] and mast cells [41]. Mast cell chemotaxis is regulated by a number of molecules including SCF, the "regulated upon activation, normal T cell expressed and secreted" (RANTES) and monocyte chemoattractant protein-1 (MCP-1) [42].

Mast cells are typically activated by cross-linking of their FcεRI by IgE/antigen complexes [27,29,43]. In addition, other molecules that can stimulate mast cell secretion include immunoglobulin free light chains [44,45], anaphylatoxins such as C3a [46,47], the human antibacterial peptides B-defensins [48] and neuropeptides [49-55] (Table **1**). The latter include substance (SP) [49], hemokinin A [50], neurotensin (NT) [56], NGF [57,58], and pituitary adenylate cyclase activating polypeptide (PACAP) [59,60]. CRH and related peptides released locally under stress may regulate mast cell function [61], especially in the skin [62]. Such neuropeptides can be secreted from local sensory nerve endings, found in close proximity to mast cells [53,57]

Mast cells can also act on precursor protein molecules from plasma and generate active peptides [63], such as histamine-releasing peptides [64] and NT, [65]. However, mast cells can also degrade NT [66] and limit its biologic effects [67].

Upon activation, mast cells secrete numerous vasoactive and pro-inflammatory mediators [18,68-72]. These include pre-formed molecules stored in secretory granules such as histamine, serotonin, TNF, kinins and proteases. In fact, mast cells are the only ''immune cells'' that store preformed TNF in their secretory granules [73]. Mast cells also synthesize and secrete arachidonic acid-derived substances, such as leukotrienes (LT), prostaglandins [74-76] and platelet activated factor (PAF) [76-78]. In addition, a number of cytokines (e.g. IL-1, 2, 5, 6, 8, 9, 13, TNF) and growth factors (e.g. bFGF, GM-CSF, M-CSF, NGF, PDGF, SCF, VEGF) [79,80] are synthesized *de novo* and released 24-48 hours after stimulation (Table **2**).

Mast cell phenotypic expression is not fixed [81,82]. Mature mast cells vary considerably in their cytokine and proteolytic enzyme content [83]. For example, in the presence of SCF, mast cells produce predominantly pro-inflammatory cytokines, whereas when IL-4 is added to SCF, they produce mostly Th2 cytokines [84]. Human umbilical cord-derived mast cells (hCBMCs) primed with IL-4 or IL-5 before stimulation with IgE release more TNF, IL-5, and granulocyte-macrophage colony-stimulating factor (GM-CSF),

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1873-4286/12 $58.00+.00

Table 1. Triggers of Mast Cell Degranulation

Acetylcholine
ATP
Adrenomedullin
Adenosine
C3α
C5α
Endothelin
Integrins
Calcitonin gene related peptide
Chemokines
Corticotropin-releasing hormone
Defensins
Estrogens
Hemokinin
IgE
IgG_1
Lysophosphatidylserine
Lysophosphatidic acid
Stem cell factor
Leptin
Mastoparan
Morphine
Hemokinin-A
Neurotensin
Nerve growth factor
0X40-ligand
Osteopontin
Pituitary adenylate cyclase Intestinal peptide
Serine proteases (e.g. trypsin, tryptase)
Peptidoglycan
Somatostatin
Substance P
Thrombin
Vasoactive intestinal peptide
S1P
Urokinase
Venoms

compared to hCBMCs maintained in SCF alone. In contrast, IL-4 enhances SCF-dependent mast cell proliferation and shifts IgE-stimulation to Th2 cytokines such as IL-3, IL-5 and IL-13, but not IL-6 [85].

SELECTIVE RELEASE OF MEDIATORS

The only way to explain mast cell involvement in many diverse cellular processes is through "differential" or "selective" release of mediators [86] (Table **3**). We first reported that mast cells secrete the content of individual granules [87], or part of their granular contents through a process associated with ultrastructural alterations of their electron dense granular core, but without degranulation [88]. This process was termed ''activation'' [89], ''intragranular activation'' [90] or ''piecemeal'' degranulation [91]. Selective release of eicosanoids without degranulation has also been reported [92-94]. We also first showed that mast cells can release specific mediators such as serotonin, without histamine [95], apparently through serotonin transport from secretory granules (800–1000 nm) to small vesicles (80-100 nm) containing high affinity serotonin-binding proteins [96]. Similarly, eosinophils transport preformed IL-4 from secretory granules into vesicles from which it is released [97]. We later reported that human mast cells stimulated by IL-1 can release only IL-6 without degranulation also through small vesicles (80 nm) [98].

IL-1, IL-9, IL-33 and TSLP

Cytokines do not trigger degranulation, but rather induce *de novo* synthesis and release of other mediators. IL-33 is one of the newest members of the IL-1 family of inflammatory cytokines [99], which was identified as a ligand for the previously orphan IL-1 receptor family member T1/ST2 [100]. IL-33 is expressed by epithelial cells, endothelial cells, fibroblasts and smooth muscle cells [101-103], as well as by mast cells after IgE-mediated activation [104]. Like IL-1, IL-33 can also induce selective release of IL-6 from mouse bone marrow-derived cultured mast cells [105]. The environmental or endogenous triggers that provoke IL-33 cellular release may be associated with infection, inflammation or tissue damage [106]. IL-33 released by necrotic cells can activate mast cells, that may act as sensors of cell injury, to release leukotrienes, IL-6 and TNF [107]. IL-33 also synergizes with IgE-dependent and IgE-independent agents to promote mast cell and basophil activation and release of IL-6 and IL-13 [108]. IL-33 can also induce naïve cord blood-derived cultured mast cells (hCBMCs) to release IL-8 and IL-13 [109]. We also showed that IL-33 augments SP-induced VEGF release from human mast cells and that IL-33 gene expression is increased in psoriasic lesions [110]. A dysregulated release of IL-33 has the potential to drive the pathophysiology of many other diseases [111], such as asthma [106], arthritis, allergic rhinitis [112], atopic dermatitis [113], and atherosclerosis [114]. IL-33 was increased in the serum of patients with systemic sclerosis and it was associated with the severity of the disease [115]. IL-33 is also produced in the central nervous system (CNS) by endothelial cells and astrocytes, where it activates microglia and may fuction as a pro-inflammatory mediator in CNS diseases [116].

IL-9 is associated with oral antigen hypersensitivity [117], promotes mast cell proliferation to the lungs [118], is upregulated in the nasal mucosa during the pollen season and correlates with tissue infiltration by eosinophils [119]. Thymic stromal lymphopoietin (TSLP), released in response to trauma, inflammation, and pathogens [120], activates human mast cell release of IL-5, IL-13, IL-6 and IL-10, but only if added together with TNF and IL-1 [120,121].

Selective release of IL-6 can also occur in response to bacterial lipopolysaccharide (LPS), in the presence of the phosphatidylinositol 3-kinase (PI3-K) inhibitor wortmannin, or when triggered by SCF [122-124]. VEGF is released selectively without degranulation from normal human cultured mast cells in response to corticotropin-releasing hormone (CRH) [125], PGE_2 [126] and MCP-1 [127].

Table 2. Mast Cell Mediators and Main Pathophysiologic Effects*

Mediators	Pathophysiologic Effects
Prestored	
Biogenic Amines	
Histamine	Vasodilation, angiogenesis, mitogenesis, pain
5-Hydroxytryptamine (5-HT, serotonin)	Vasoconstriction, pain, superficial skin flushing
Chemokines	
IL-8 (CXCL8), MCP-1 (CCL2), MCP-3 (CCL7), MCP-4, RANTES (CCL5), Eotaxin (CCL11)	Chemoattraction and tissue infiltration of leukocytes
Cytokines	
Tumor necrosis factor	Inflammation, cell apoptosis
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
Nucleotides	
ATP, Mitochondrial DNA	Mast cell and PPM activation, inflammation
Peptides	
Adrenomedulin	Tumor cell recruitment, mast cell activation
Angiogenin	Neovascularization
Corticotropin-releasing hormone	Inflammation, vasodilation, mast cell activation
Endorphins	Analgesia
Endothelin	Sepsis
Kinins (bradykinin)	Inflammation, pain, vasodilation, mast cell activation
Leptin	Food intake regulator
Neurotensin	Inflammation, pain, vasodilation, mast cell activation
Neurotrophin 3	Nerve growth, mast cell proliferation
Osteopontin	Bone cell apoptosis, mast cell activation
Renin	Angiotensin synthesis
Somatostatin	Anti-inflammatory (?), mast cell activation
Substance P	Inflammation, pain, mast cell activation
Urocortin	Inflammation, vasodilation, mast cell activation
VEGF	Neovascularization, vasodilation
Vasoactive intestinal peptide	Vasodilation, mast cell activation
Proteoglycans	
Chondroitin sulfate	Cartilage synthesis, anti-inflammatory, mast cell inhibition
Heparin	Angiogenesis, nerve growth factor stabilization Mast cell inhibition
Hyaluronic acid	Connective tissue, nerve growth factor stabilization

(Table 2) Contd....

Mediators	Pathophysiologic Effects
De novo synthesized	
Cytokines	
Interleukins (IL)-1,2,3,4,5,6,8,9,10,13,16,18,33	Inflammation, leukocyte migration, pain
IFN- α , IFN- β, IFN-γ; MIF; TGFβ; TNF-α,	Inflammation, leukocyte proliferation/activation
MIP-1α, MCP-1	
Growth Factors	
SCF, GM-CSF, β-FGF, neurotrophin 3, NGF,	Growth of a variety of cells, mast cell proliferation or activation
PDGF, TGFβ, VEGF	
Nitric oxide	Vasodilation, mast cell inhibition
Phospholipid metabolites	
Leukotriene B_4	Leukocyte chemotaxis
Leukotriene C_4	Vasoconstriction, pain
Platelet activating factor	Platelet activation, vasodilation
Prostaglandin D_2	Bronchonstriction, pain

* There are differences in the expression of mediators between human and rodent mast cells.
β-FGF, β-fibroblast growth factor; BDNF, brain derived neurotrophic 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.

Table 3. Selective Release of Mast Cell Mediators*

Stimuli	MC Type	Mediators Released	Mediators NOT Released	Pathophysiological Action	References
ENDOGENOUS					
CD30 ligands	hCBMC	IL-8, MIP-1α, MIP-1β	H	Inflammation	[128]
CD8 ligands	RPMC	TNF, NO	H	T cell interaction	[355]
CRH	hCBMC	VEGF	H, tryptase, IL-8	Inflammation	[125]
Endothelin-1 -3	RMMC	TNF, IL-12↑	IL-4, IL-10, IL-13↓*	Th1 immunity	[356]
IL-1	hCBMC	IL-6, IL-8, TNF	H, tryptase	Inflammation	[98]
IL-1β	RPMC	NO	PAF, H	Inflammation	[357]
IL-12	P815	IL-13		Host defence against bacteria	[358]
IL-12	RPMC	IFN-γ	H, HA	Th1 immunity	[359]
IL-33	LAD2, RPMC	VEGF, IL-13	HA	Inflammation	[110,130]
LTC_4/LTD_4	IL-4-primed hCBMC	TNF, MIP-1α, IL-5	H	Non-IgE mediated inflammation	[360]
Monomeric IgE	BMMC	IL-6	H, LTC_4	Mast cell survival	[361]
PGE_2	RPMC	IL-6	H, TNF	Cytoprotection	[362]
SCF	BMMC	IL-6	H, LTC_4, TNF	Mast cell development	[124]
SDF	hCBMC	IL-8	H, GM-CSF, IFN-γ, IL-1β	Endothelial transmigration	[129]
Thrombin	BMMC	IL-6	Serotonin, TNF	Anticlotting	[363]

(Table 3) Contd....

Stimuli	MC Type	Mediators Released	Mediators NOT Released	Pathophysiological Action	References
TSLP+IL-1+TNF	hCBMC	IL-5, IL-13, IL-6, IL-10	H	Inflammation	[120]
Urocortin	hCBMC	IL-6	H, tryptase, IL-8, VEGF	Inflammation	[364]
EXOGENOUS/PHARMACOLOGICAL					
Amitriptyline	RPMC	Serotonin	HA	Headaches	[95]
Cholera Toxin	RPMC	IL-6	HA, TNF	Inflammation	[365]
Clostridium difficile Toxin A	RPMC	TNF	HA	GI tract inflammation	[366]
CpG DNA	BMMC	TNF, IL-6	HA, IL-4, IL-12, GM-CSF, IFN	Host response to bacteria	[367]
H. pylori VacA Toxin	BMMC	IL-6, IL-8, TNF	HA	Gastric injury	[140]
LPS (TLR-4)	RPMC	IL-6	HA	Bacterial infection	[122]
PMA	BMMC	VPF/VEGF	5HT	Angiogenesis	[368]
S.a.peptidoglycan (TLR-2)	hCBMC	HA, IL-1β, RANTES, LTC_4	IL-6	Exacerbation of asthma by bact. infection	[137]
Suboptimal FcεRI stimulation	BMMC	MCP-1, HA low	IL-10, HA	Chemokines >>Cytokines /HA	[369]
Viruses (TLR-3,5,9)	FSMC	TNF, IL-6	HA	Recruitment of other immune cells	[141]

* There are differences in the expression of mediators between human and rodent mast cells.
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; TSLP, thymic stromal lymphopoietin; VEGF, vascular endothelial growth factor.

PGE_2 leads to release of MCP-1 without histamine and without degranulation [125]. CD30 ligands lead to release of the chemokines IL-8 and MCP-1 also without degranulation [[127,128]. Stromal cell-derived factor-1 alpha (SF-1α) selectively produces IL-8 from human mast cells without degranulation [129] and IL-33 induces IgE-independent IL-13 release [130].

TLR Activation

Activation of mast cell TLR, is critical in innate and acquired immunity [131,132], and leads to release of different cytokines [133]. TLR-2 and TLR-4 activation have a synergistic action with antigen in enhancing cytokine production from rodent mast cells [134]. Rodent mast cell TLR-4 activation by LPS induces TNF release without degranulation [135]. TLR-4 is also activated by the extra domain A of fibronectin to release several cytokines, including TNF [136]. Furthermore, LPS induces secretion of IL-5, IL-10 and IL-13, but not GM-CSF, IL-1 or LTC_4 by human mast cells [137,138]. In contrast, staphylococcal peptidoglycan induces degranulation and histamine release through activation of TLR-2 [137,139]. Unlike TLR-4 activation, TLR-2 activation produces IL-4, IL-6 and IL-13, but not IL-1; instead LPS produces TNF, IL-1, IL-6 and IL-13, but not IL-4 or IL-5, again without degranulation [140]. TLR 3, 7 & 9 activation by poly-oligodeoxynucleotide and the unmethylated consensus DNA sequence, CpG motif, in bacteria and viruses induces release of TNF and IL-6 without degranulation from fetal rat skin-derived mast cells [141]. Human mast cells produce IL-6 through viral TLR-9 activation [142], while they produce interferon (IFN) following TLR-3 activation by double-stranded RNA [143].

Mast cells are also involved in the maturation of Th17 cells, recognized as key cells in autoimmune disorders [144]. For instance, mast cell-derived transforming growth factor β (TGFβ) and IL-6 are necessary for the production of Th17 cells [145], while TNF and vasoactive intestinal peptide (VIP) drive IL-6-independent Th17 cell maturation [145-147]. Osteopontin stimulates mast cells [148], is secreted from mast cells [148] and is involved in Th17 cell maturation [149,150]. Moreover, IL-9 producing mast cells also drive Th17 cells [151,152].

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 [153]. Mast cells interact with T cells [154,155]. In particular both mouse [156,157] and human [158,159] mast cells can superactivate T-cells through TNF and direct cell to cell contact. A subset of mast cells highly expressing both FcεRI and MHC II [7], can function as antigen presenting cells and initiate the immune response [8,160,161]. Basophils, the circulatory counterpart of mast cells, can also act as Th2-inducing antigen-presenting cells [162,163] [164,165] and co-operate with dendritic cells for optimal Th2 responses [166].

Novel Means of Communication

Mast cells appear to have other ways of communicating with other cells than release of mediators. Mast cell-derived heparin "microparticles" contain and deliver TNF to lymph nodes [167].

Conversely, T cells release "microparticles" that stimulate human mast cell degranulation and IL-8 release [168]. Mast cells may also be able develop nanotubules that make contact with other cells as shown for PC12 cells [169] and T-cells [170]. Mast cells can also release nucleic acids in "pathogen traps" [171] like eosinophils [172] and polymorphonuclear leukocytes [173], as well as inside "exosomes" [174], small membrane-enclosed vesicles that transfer mRNA and microRNAs [175,176].

CORONARY ARTERY DISEASE

Increasing evidence indicates that atherosclerosis involves inflammation that may be more important than the stable cholesterol plaque [177] because the secondary inflammatory plaque is more likely to break off and cause infarcts [178-181]. Both intimal and arterial adventitia inflammation can influence plaque vulnerability [182]. Specifically, increased serum levels of C-reactive protein (CRP) [183] and IL-6 [183,184], especially intracardiac IL-6 [185], constitute independent risk factors for coronary artery disease (CAD) [186]. Saturated fatty acids can activate TLRs in the brain and generate an inflammation state, as well as metabolic inbalance and insulin resistance [187]. Genetic loss of TLR4 can ameliorate insulin resistance [188,189].

Mast cells are present in the heart [190], accumulate in the rupture prone shoulder region of atheromas [191,192] and participate in coronary artery spasm [193]. Coronary artery mast cell numbers also correlate with the incidence of plaque rupture and erosion [194,195]. IL-1 expressed from the secondary inflammatory plaque could also stimulate mast cells to release IL-6, selectively [196]. Atherosclerotic plaque rupture [180,197], especially of a thin-cap fibroatheroma [198], or superficial erosion leading to an occluding thrombus of a coronary artery, clinically manifest themselves as acute coronary syndromes (ACS); that present as unstable angina, acute MI or sudden cardiac death [199].

Adventitial mast cells are also localized close to sensory nerve endings in atherosclerotic coronary arteries [200], and mast cell content correlates with the number of NGF-positive nerve fibers in the adventitia of human coronary atherosclerotic plaques [201]. SP could activate adventitial mast cells and promote intraplaque hemorrhages, actions that could be prevented by co-administration of an NK-1 receptor blocker, and did not develop in mast cell deficient $ApoE^{-/-}$ mice [201]. NT-immunoreactive fibers are also present in the heart [202] and NT can cause coronary vasoconstriction [203]. NT is known to stimulate the secretion of histamine from mast cells [56] and in isolated heart preparations [204]. Local NT, as well as CRH secreted following acute stress, trigger cardiac mast cell degranulation blocked by an NT-receptor antagonist [204]. Acute stress leads to elevated plasma IL-6 in rodents [205,206]. This increased serum IL-6 is greater in $ApoE^{-/-}$ atherosclerotic mice [207] but is absent in mast cell-deficient mice [207]. Serum IL-6 was also increased in ischemia-reperfusion (I/R) in mice and the levels of IL-6 correlated with the extent of cardiac tissue necrosis; in contrast, mast cell deficient mice had normal IL-6 levels and less cardiac tissue necrosis [208]. The CRH-related peptide urocortin can also stimulate IL-6 release from neonatal cardiomyocytes [209]. TNF upregulates IL-6 in infiltrating leukocytes and leads to myocyte intercellular adhesion molecule-1 (ICAM-1) induction and subsequent neutrophil-induced injury [210]. Human coronary artery specimens contain TNF-rich activated mast cells [211]. Local release of preformed and newly synthesized TNF from cardiac mast cells [73], could recruit leukocyte during ischemia [212]. Matrix metalloproteinase-1 (MMP-9) is also released exclusively from mast cells during acute stress in mice [213].

The mast cell degranulator compound C48/80 promoted atherosclerotic plaque in $ApoE^{-/-}$ mice, increased the degree of lumen stenosis, proliferation of SMCs, magrophage aggregation, and plaque angiogenesis [214]. In addition to $Apo^{-/-}$ mice, $Ldlr^{-/-}$ mice are also atherosclerosis-prone; however mast cell deficient $Ldlr^{-/-}$ $kit^{w\text{-}sh/w\text{-}sh}$ mice have decreased atheroma size, lipid deposition, T-cell and macrophage numbers [215]. Adoptive transfer of normal mast cells in $Ldlr^{-/-}$ $kit^{w\text{-}sh/w\text{-}sh}$ mice restored atherogenesis, but not when IL-6 and interferon-γ (IFN-γ) deficient mast cells were used [215]. More recently, mast cell-deficient mice have lower serum cholesterol, triglyceride levels, atherogenic apoB-containing particles and serum pre-high-density lipoprotein, as well as less vascular inflammation [216].

Gene array analysis of human mast cells activated by IgE showed overexpression of numerous inflammation-related genes [217]. Proteases such as tryptase, chymase and cathepsin-D are secreted from mast cell granules and can stimulate protease-activated receptors (PAR) inducing microleakage and widespread inflammation [218,219]. Moreover, proteases could act on plasma albumin to generate histamine-releasing peptides [64,220] that would further propagate mast cell activation and inflammation. Proteases could degrade the endothelial basement membrane, loosen the attachment of endothelial cells to the wall of the atherosclerotic plaque and lead to plaque erosions [221]. Mast cell- derived tryptase also damages the fragile inner plaque microvessels and contributes to microvascular leakage [222], leading to intraplaque hemorrhages and the generation of unstable lesions [223]. Chymase and cysteine proteases such as Cathepsin S and L [224] are also involved in abdominal aortic aneurysm (AAA) expansion [225,226]. Tryptase stimulates calcium-independent phospholipase A2 (iPLA2) [227], leading to the synthesis of membrane phospholipid-derived inflammatory mediators, such as platelet activating factor (PAF) [228]. Mast cells also synthesize PAF [229,230]. PAF stimulates platelets [231], thus promoting thrombus formation and increasing the risk of MI.

Mast cell chymase activates pro-MMP-1, which is also found in atherosclerotic lesions [232]. Human mast cells also secrete MMP-9 on contact with activated T-cells [233]. Chymase acts as angiotensin converting enzyme (ACE) which is insensitive to ACE inhibitors [234] and leads to formation of angiotensin II (Ang II) [235]. Cardiac mast cells also contain renin, which they secrete during myocardial ischemia [236,237], thus contributing to availability of Ang I, the substrate to be acted upon by chymase. Ang II is a potent coronary vascoconstrictor [238,239] and pro-inflammatory peptide [240]. It also causes arrhythmias [237], fibrosis [241], and endothelin release [242], as well as SMC [243] and cardiomyocyte apoptosis [244]. Ang II also enhances angiogenesis by inducing VEGF expression [245].

Mast cells could contribute to CAD through additional mediators. The number of 5-lipooxygenase (5-LO) expressing cells including mast cells is markedly increased in advanced lesions [246]. 5-LO activity is increased in arterial walls of atherosclerotic arteries [246] and leads to formartion of leukotrienes, which exhibit strong pro-inflammatory activities in cardiovascular tissues [247]. Leukotriene B_4 receptor (BLT-R) antagonism, as well as deficiency of one 5-LO allele, were shown to be protective in atherosclerosis susceptible mouse strains [246]. Histamine [248] is associated with atherosclerosis and CAD [249]. Histamine increases tissue factor (TF) expression and activity in human aortic endothelial cells and vascular SMC [250]. Elevated TF antigen and activity have been detected in plasma and in atherectomy specimens of patients with unstable angina [251]. TF binds activated factor VII, which in turn activates factor X leading to formation of thrombin, which also activates mast cells [219]. Histamine also increases vascular permeability to lipoproteins [252] and can induce coronary spasm [253]. Moreover, histamine can sensitize nerve endings [254] and lead to pro-arrhythmogenic effects [255-257]. Histamine also induces IL-6 [258] and IL-8 [259] release from human coronary endothelial cells, is enhanced by LPS and TNF-α [260]. In addition, histamine causes intimal thickening in a mouse model of atherosclerosis [261].

Mast cells produce endothelin-1 (ET-1) [262], a 21–amino acid peptide with mitogenic and vasoconstrictive properties [263,264]. ET-1 is responsible for the resting tone in atherosclerotic coronary arteries [265]. Mast cell activation results in increased expression of ET-1 mRNA in cultured endothelial cells [266]. Administration of ET-1 to blood-perfused, isolated rat hearts resulted in extensive mast cell degranulation, increased MMP-2 activity and collagen degradation [267]. Mast cells also lead to degradation of ET-1 peptide through mast cell proteases [9,266]. Peripheral ET-1 is increased in patients with advanced atherosclerosis and in coronary circulation of patients with early atherosclerosis and coronary endothelial dysfunction [268-270]. Long term administration of ET-1 receptor antagonists improves coronary endothelial function in patients with early atherosclerosis [271].

Oxidative stress plays an important role in pathogenesis of CAD, especially during post-ischemia reperfusion [272,273]. Reactive oxygen species (ROS) activate mast cells [274], and so does oxidized LDL [275]. Advanced glycation end products (AGEs) also accumulate in obesity and can activate mast cells, thus contributing to production of ROS, increased formation of AGEs and increased low-grade inflammation typical of chronic diseases [276]. Myocardial I/R-related oxidative stress leads to the release of TNF which can be prevents by mast cell inhibitors [277]. Furthermore, the use of the superoxide dismutase mimetic, M-40403, prevents mast cell degranulation following reperfusion of ischemic rat heart [278]. ROS also induce the release of SP from sensory nerves [279], which results in mast cell degranulation with subsequent renin release and angiotensin formation locally causing sustained reperfusion arrhythmias [280]. Acetaldehyde produced during I/R stimulates SP and renin release from cardiac synaptosomes and mast cells, respectively, and these actions are blocked by NK-1 blockers [280]. The complement fragment C5a is important in scar formation in MI [281] and in I/R injury [282]. C5a is a known chemotactic factor for mast cells [46], and it also triggers human cardiac mast cell degranulation [283,284].

Adenosine acts on mast cells via A2a and A2b receptors causing degranulation [285] and the release of IL-8 [286], and VEGF [287]. Activation of A3 receptors also causes more mast cells to degranulate [288,289], while A3R $^{-/-}$ mice are tolerant to I/R injury [289].

Obesity

There is little doubt that obesity contribudes to CAD [290,291]. Increasing evidence now indicates that obesity is associated with a low-grade inflammation of white adipose tissue (WAT) leading to insulin resistance, impaired glucose tolerance and even diabetes [292]. TNF released from immune cells found in adipose tissue mediates insulin resistance through tyrosine phosphorylation of Insulin Receptor Substrate (IRS) proteins, which are crucial in mediating insulin action [293,294]. Lack of TNF ligand or the p-55 TNF receptor improves insulin sensitivity and glucose homeostasis suggesting that this inflammatory response is important in the regulation of insulin action in obesity [295,296]. In addition, elevated levels of acute phase reactants, such as C-reactive protein (CRP) and plasminogen activator inhibitor-1 (PAI-1) are associated with increased risk for development of Type II diabetes [297]. Treatment of obese T2D patients with etanercept, a TNF-α antagonist results in reduced blood glucose and increased levels of adiponectin [298].

Obese adipose tissue is associated with accumulation of inflammatory cells including macrophages [299], T-cells [300] and mast cells [301,302]. Mast cells could contribute to obesity by promoting angiogenesis. WAT and muscle tissues from wild-type obese mice contain significantly more microvessels immunostaining of CD31 and mast cells than those from wild–type lean mice [302]. These microvessels supply the WAT with nutrients and also provide a path for leukocyte infiltration followed by adipokine release [303,304]. Kit$^{W\text{-}sh/W\text{-}sh}$ mast cell deficient mice fed a Western diet for 12 weeks gain significantly less body weight, have improved glucose intolerance and have reduced adipose tissue, less IL-6 and IFN-γ, as well as reduced blood leptin and insulin levels as compared with congenic wild-type controls [302]. Leptin resistance has been implicated in the pathogenesis of obesity-related complications involving abnormalities of lipid metabolism [305]. Both leptin and leptin receptors are expressed by human mast cells [306]. Insufficient amounts or action of leptin decreases metabolic rate [307] and causes hyperinsulinemia [308].

Potential Mast Cell Inhibitors and Treatment Approaches

Therapeutic interventions to inhibit inflammatory pathways in CAD and obesity have generated encouraging results in mouse models and human trials [309-311]. A recent study showed that treatment of obese Type II diabetics with the TNF blocker Etanercept, resulted in improved glycemia and increased adiponectin levels [298]. Thiazolidienes (TZDs) which are potent agonists of Peroxisome proliferator-activated receptor-gamma (PPARγ) restore lipogenic function to adipocytes, and are also known to possess anti-inflammatory properties [312,313]. The beneficial effect of acetyl salicylic acid in CAD may not be its anti-clotting, but rather its anti-inflammatory effect [314-316]. Moreover, recent evidence indicates that statins also possess anti-inflammatory actions [317], while other anti-inflammatory drugs are being developed mostly by targeting distinct molecules. Niacin is well known for its ability to reduce total cholesterol and LDL, while increasing HDL [318], but it causes intense flush and itching [319] that limits compliance severely. Recent evidence also indicates that niacin may prevent release of inflammatory mediators from adipocytes [318].

Unfortunately, there are no effective, clinically available mast cell inhibitors (Table **4**). Disodium cromoglycate (cromolyn) significantly inhibits histamine secretion from rodent mast cells, but it is a very weak inhibitor of human mast cells [320,321]. The histamine-1 receptor antagonists loratadine/desloratadine, cetirizine/levocetirizine, azelastine, and mezolastine can partially inhibit the release of mediators from human mast cells to various degrees [322,323]. The antihistamine ketotifen, also partially inhibits mast cells [324], but is only available for allergic conjunctivitis in the US. The newest antihistamine rupatadine, which has anti-PAF and anti-eosinophilic properties (not available in the US), also exhibits mast cell inhibitory actions [78].

A number of chymase inhibitors under development are not clinically available yet [325], while one tryptase inhibitor, APC 2059 has only been tested for asthma with mixed results [326,327].

Histamine can inhibit its own synthesis and release through auto-activation of H_3 receptors in the CNS [328] and H_4 receptors in the periphery [329] and H3 receptor agonists [330] may be useful in the treatment of CAD. Chondroitin sulfate [321] and heparin [331], the major constituents of mast cell granules, inhibit human mast cell secretion. In contrast IL-10 appears to have divergent effects depending on the mast cell type and stimulus [332]. The natural chymase inhibitors alpha 1-antitrypsin and secretory leukocyte protease inhibitor (SLPI) inhibit histamine release from human cells [333]. Nitric oxide (NO) blocks FcεRI-induced cytokine secretion [334].

Peptide sequences of the complement fragment C3a (C3a7 and C3a9) were reported to inhibit FcεRI-induced immediate and late phase mediator secretion by binding to the FcERI β- chain [335].

Certain naturally occurring flavonoids, such as luteolin and quercetin, have potent anti-oxidant, anti-inflammatory [336,337], and mast cell inhibitory actions [338,339]. Quercetin can also inhibit IL-6 release in response to IL-1 [196]. A recent paper reported that quercetin can accumulate in mitochondria [340], implying that they may be involved in the regulation of mast cell degranulation. In fact, we showed that increased expression of mitochondrial uncoupling protein 2 (UCP2) is associated with inhibition of mast cell histamine production and degranulation [341]. Conversely, inhibi-

Table 4. Compounds Inhibiting Mast Cell Functions

Class Compound	Inhibition of Degranulation	Inhibition of Late Phase Cytokine Release	Inhibition of Eosinophil Action
Chromones			
Cromolyn	+/-	-	-
Lodoxamide	+	+	-
Flavonoids			
Luteolin	++	++	-
Quercetin	++	++	-
Enzyme inhibitors			
α-1 antitrypsin	+	+/-	-
Anti-IgE *	+	+	-
Chymase inhibitors	-	-	-
H_1 receptor antagonists			
Azelastine	+	+	-
Desloratadine	+	+/-	-
Hydroxyzine	+	+/-	-
Ketotifen	+	+	+
Rupatadine	+	+	++
Proteoglycans			
Chondroitin sulfate	+	+	-
Heparin	+	+	-
Methylthiosalicylate	+	+	-
Others			
IL-10	+/-	+/-	
Nitric oxide	+/-	+/-	-
Cortisone	-	++	+++
Oxidized polyamines	+	+	-

*This is an indirect action neutralizing circulating IgE but often leads to rebound IgE elevations

tion or downregulation of Dynamin Related Protein 1 (Drp1), a cytoplasmic protein responsible for mitochondrial fission and translocation, blocks mast cell degranulation [342]. A recent paper also reported that inhibiting mitochondrial autophagy also blocks mast cell activation [343].

The 7-luteolin-glycoside has its own independent ability to reduce total cholesterol [344]. Moreover, quercetin mimics the action of glucagon-like peptide-1, a promising agent for the treatment of type II diabetes [345]. A novel formulation, CardioNiacin® which is presently under development contains slow release niacin, with a combination of unique flavonoids which prevent niacin induced flush [346-348], and reduce IL-6 [196].

CONCLUSION

Mast cells clearly participate in the induction and/or propagation of certain inflammatory diseases, such ACS. These findings may also explain why many cases of ACS develop in the absence of atherosclerosis [349-351]. Some of these cases may be precipitated by acute stress [349,352,353] or be associated with coronary hypersensitivity, known as "Kounis syndrome" [354]. Effective inhibition of release of mast cell mediators could have unique 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 CAD, obesity and other inflammatory disorders.

ACKNOWLEDGMENTS

Aspects of our work discussed here were supported in part by US National Institutes of Health (NIH) grants: AR47652, NS71361, NS55681 and NS66205 to TCT. Drs. Konstantinos-Dionysios Alysandratos and Asimenia Angelidou are recipients of postgraduate scholarships from the Hellenic State Scholarships Foundation

(Athens, Greece). Bodi Zhang is partially supported by a graduate fellowship from Galenica, SA (Athens, Greece).

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, as well as patent applications 11/99991; 12/151,268 covering the role of mast cells in inflammatory diseases, including CAD.

ABBREVIATIONS

AAA	=	Abdominal aortic aneurysms
ACS	=	Acute coronary syndrome
Bcl10-Malt1	=	B cell lymphoma 10-mucosal-associated lymphoid tissue 1
BDNF	=	Brain-derived neurotrophic factor
CAD	=	Coronary artery disease
CRH	=	Corticotropin-releasing hormone
CRHR	=	Corticotropin-releasing hormone receptor
CRP	=	C-reactive protein
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
IRS	=	Insulin receptor substrate
5-LO	=	5-lipooxygenase
LPS	=	Lipopolysaccharide
LT	=	Leukotriene
MBP	=	Myelin basic protein
MCP-1	=	Monocyte chemoattractant protein-1
MMP	=	Matrix metalloproteinase
NGF	=	Nerve-growth factor
NK	=	Neurokinin
NT	=	Neurotensin
PACAP	=	Pituitary adenylate cyclase activating polypeptide
PAF	=	Platelet activating factors
PAI	=	Plasminogen activator inhibitor-1
PAR	=	Protease activated receptors
PI3-K	=	Phosphatidylinositol 3-kinase
PPARγ	=	Peroxisome proliferator-activated receptor-gamma
PTEN	=	Phosphatase and tensin homologue deleted on chromosome ten
RANTES	=	Regulated upon activation, normal T cell expressed and secreted
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
WAT	=	White adipose tissue

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Received: December 2, 2011 **Accepted: January 19, 2012**