HOSPITAL CHRONICLES 2006, SUPPLEMENT: 192–196

The Role of Mast Cells in Acute Coronary Syndromes

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ABSTRACT

OBJECTIVE: Review evidence supporting the role of mast cells in cardiovascular pathophysiology. **BACKGROUND:** Cardiovascular inflammation has emerged as a key pathogenetic factor in coronary artery disease (CAD) and myocardial ischemia reperfusion (IR) injury. IR complicates all forms of coronary artery revascularization. Cardiac mast cells have been implicated in CAD, IR and myocardial infarction (MI) through the release of pro-arrhythmogenic and inflammatory mediators, especially interleukin-6 (IL-6), considered an independent risk factor. **METHODS:** We reviewed relevant literature and summarized our own findings. **RESULTS:** We showed that CAD is associated with high intracoronary release of IL-6. Acute stress triggers mast cell- dependent release of histamine and IL-6. Moreover, acute stress in ApoE -/- mice leads to ischemia. Mast cells express corticotropin-releasing-hormone (CRH) receptors, activation of which leads to selective release of vascular endothelial growth factor (VEGF), an isoform of which is vasodilatory. In a randomized prospective study, we investigated serum IL-6 levels and cardiac tissue susceptibility in the mast cell deficient (W/Wv) mice (n=12) and their normal littermates (+/+). When the left coronary artery (LCA) was ligated followed by 6 hr of reperfusion IL-6 levels increased significantly after reperfusion only in the +/+ mice, but not in mast cell deficient W/Wv mice; cardiac muscle viability was significantly higher in W/Wv than the +/+ mice. **CONCLUSION:** These results support targeting selective inhibition of cardiac mast cell activation as prophylactic therapy in clinical situations involving myocardial inflammation and/or revascularization.

ABBREVIATIONS:
CAD: coronary artery disease;
CRH: corticotropin releasing hormone;
IL-6: interleukin 6;
IR: ischemia reperfusion;
LCA: left coronary artery;
MI: myocardial infarction;
VEGF: vascular endothelial growth factor

KEY WORDS: *inflammation, mast cells, stress, vascular permeability*

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1. SELECTIVE RELEASE OF MAST CELL MEDIATORS

Mast cells derive from a distinct precursor in the bone marrow [1] and mature under local tissue microenvironmental factors [2]. Mast cells are necessary for the development of allergic reactions, through crosslinking of their surface receptors for IgE (FcεRI), leading to degranulation and the release of vasoactive, pro-inflammatory and nociceptive mediators that include histamine, cytokines and proteolytic enzymes [3,4] (Table 1). The multitude of mediators that could be secreted, especially in response to many non-immunologic triggers (Table 2) has given rise to new speculations about the possible role of mast cells in immune responses, especially acquired immunity [5] and inflammation [6].

Aspects of the work discussed were supported in part by grants from US NIH #AR47652 and Theta Biomedical Consulting and Development Co., Inc. (Brookline, MA) TCT has been awarded US patents #5,250,529; #6,020,305; #5,648,350; #5,855,884; #5,821,259; #5,994,357; #6,624,148 covering the use of CRH and mast cell blockers in inflammatory diseases.

TABLE 1. Mast cell Triggers

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

Unlike allergic reactions, mast cells are rarely seen to degranulate during autoimmune [7] or inflammatory processes [8]. Instead, mast cells can secrete mediators without overt degranulation [9], through differential or selective release [10], probably regulated by the action of distinct protein kinases on a unique phosphoprotein [11,12]. In such cases, mast cells undergo ultrastructural alterations of their electron dense granular core indicative of secretion, but without overt degranulation, a process that has been termed "activation" [13-15] "intragranular activation" [16] or "piecemeal" degranulation [17]. Selective release has been reported for a number of mediators [18-20], especially serotonin [10], eicosanoids [21-23] or IL-6 [24-27]. In fact, we showed that interleukin-1 (IL-1) can stimulate human mast cells to release IL-6 selectively without degranulation, through a unique process utilizing 40-80 nm vesicles unrelated to the secretory granules (800-1000 nm) [28]. We also recently showed that corticotropin releasing hormone (CRH) secreted under stress can stimulate human mast cells through specific CRH receptors to release vascular endothelial growth factor (VEGF) selectively [29].

These findings suggest that mast cells may also be involved in inflammatory diseases [6,30] that include migraines [31] and cardiovascular disease [32].

2. CARDIOVASCULAR INFLAMMATION

Increasing evidence implicates acute psychological stress and cardiac mast cells in cardiovascular pathology, especially unstable angina and silent myocardial ischemia (MI). MI occurring without angina on presentation now appears to be a sizable portion of the MI population [33-36]. Allergic angina and MI have also been reported [37]. Mast cells have also recently been implicated in coronary microembolization and cardiomyocyte apoptosis [38]. There is growing evidence that cardiac mast cells [39] participate in the development of atherosclerosis, coronary inflammation and cardiac ischemia. Mast cells have been identified in coronary arteries during spasm [40], and accumulate in the shoulder region of human coronary atheromas, especially in association with plaque rupture [32,41,42]. The human mast cell proteolytic enzyme chymase has been shown to be the main cardiac source of converting enzyme generating the coronary constrictor angiotensin II [43]. Chymase can also promote cholesterol removal from HDL and deposition on foam cells [44-46]. Mast cells tryptase can induce wider spread inflammation through stimulation of protease-activated receptors (PAR) [47]. Tryptase is also a biomarker in patients with stable CAD [48]. Cardiac mast cell-derived histamine [49] can constrict the coronaries [50] and can sensitize nerve endings [51]; this action is rendered probable by the recent findings showing adventitial mast cells localized close to nerve endings in atherosclerotic coronary arteries [52].

Acute stress induced rat cardiac mast cells activation documented morphologically [53] It was later shown that acute stress induced histamine release from mouse heart [54], as well as serum histamine and IL-6 elevations [54,55]; these were greater in apolipoprotein E (ApoE) knockout mice that develop atherosclerosis, but were still entirely dependent on mast cells [54,55]. These findings are significant since serum IL-6 elevations in patients with acute MI were shown to derive primarily from the coronary sinus [56]. Both histamine [57] and IL-6 [58] are significant predictive risk factors of coronary events.

We also recently showed that ischemia reperfusion in mice

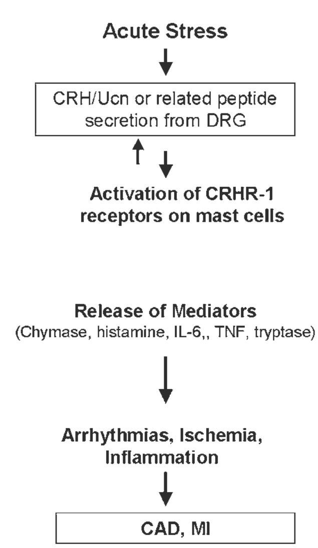

FIGURE 1. Schematic representation of the sequence of events that may lead to cardiac mast cell activation and neurogenic inflammation, leading to CAD.

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, MCP-1, MCP-3, MCP-4, RANTES	Chemoattraction and tissue infiltration of leukocytes
Enzymes	
Arylsulfatases	Lipid/proteoglycan hydrolysis
Carboxypeptidase A	Peptide processing
Chymase	Tissue damage, angiotensin II synthesis, cholesterol liberation
Kinogenases	Synthesis of vasodilatory kinins, pain
Phospholipases	Arachidonic acid generation
Tryptase	Tissue damage, activation of PAR, inflammation, pain
Peptides	
Corticotropin-releasing hormone (CRH)	Inflammation, vasodilation
Endorphins	Analgesia
Endothelin	Sepsis
Kinins (bradykinin)	Inflammation, pain, vasodilation
Somatostatin (SRIF)	Anti-inflammatory (?)
Substance P (SP)	Inflammation, pain
Vasoactive intestinal peptide (VIP)	Vasodilation
Urocortin	Inflammation, vasodilation
Vascular endothelial growth factor (VGEF)	Neovascularization, vasodilation
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)-1,2,3,4,5,6,9,10,13,16	Inflammation, leukocyte migration, pain
INF-γ; MIF; TNF-α	Inflammation, leukocyte proliferation/activation
Growth Factors	
SCF, GM-CSF, b-FGF, NGF, VEGF	Growth of a variety of cells
Phospholipid metabolites	
Leukotriene B4 LTB4	Leukocyte chemotaxis
Leukotriene C4 (LTC4)	Vasoconstriction, pain
Platelet activating factor (PAF)	Platelet activation, vasodilation
Prostaglandin D2 (PGD2)	Bronchonstriction, pain
Nitric oxide (NO)	Vasodilation

CRH= corticotropin-releasing hormone, TGF-β= transforming growth factor-β, CSF= colony stimulating factor, TNF-α= tumor necrosis factor-α, INFγ= Interferon-γ, SRIF= somatomedin release inhibitory factor, somatostatin, MIF= macrophage inflammatory factor, GM-CSF= granulocyte monocyte-colony stimulating factor, b-FGF= fibroblast growth factor, NGF= nerve growth factor, SCF= Stem cell factor, VEGF= vascular endothelial growth factor.

increased serum IL-6 and myocardial necrosis, but not in W/W^{v} mast cell deficient mice [59]. Such results have prompted editorials implicating mast cells CAD and MI [60].

CONCLUSION

In summary, the mast cell has emerged as a unique immune cell that could be activated by many non-immune processes, including acute stress [61,62], and could participate in CAD and MI (Figure 1).

ACKNOWLEDGMENTS

We thank Ms. Jessica Christian for her word processing skills.

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