Review

Mast cells squeeze the heart and stretch the gird: Their role in atherosclerosis and obesity

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Mast cells are crucial for the development of allergic and anaphylactic reactions, but they are also involved in acquired and innate immunity. Increasing evidence now implicates mast cells in inflammatory diseases through activation by non-allergic triggers such as neuropeptides and cytokines. This review discusses how mast cells contribute to the inflammatory processes associated with coronary artery disease and obesity. Animal models indicate that mast cells, through the secretion of various vasoactive mediators, cytokines and proteinases, contribute to coronary plaque progression and destabilization, as well as to diet-induced obesity and diabetes. Understanding how mast cells participate in these inflammatory processes could help in the development of unique inhibitors with novel therapeutic applications for these diseases, which constitute the greatest current threat to global human health and welfare.

Non-allergic pathophysiological functions of mast cells

Mast cells were first described by Paul Ehrlich in various tissues, but their function remained unknown until the 1950s, when they were implicated in the pathogenesis of allergic reactions [1]. Understanding of the biological significance and clinical implications of mast cells has increased in the past few years. Mast cells are now considered to play an important role in a wide spectrum of biological processes ranging from innate and acquired immunity [2,3] to inflammation [4], infection [5], and antigen presentation [6], as well as angiogenesis and tissue repair [7]. Knowledge of the function of mast cells has been augmented by the discovery that they originate from hemopoietic stem cells [8] and white adipose tissue (WAT) [9]. These progenitor cells migrate into tissues, where they differentiate under the influence of various microenvironmental conditions, principally stem cell factor (SCF) [10]. Mature, resident mast cells contain many granules rich in histamine and heparin.

Mast cells have been reported in the heart [11], and cardiac mast cells have been shown to differ from other connective tissue, such as skin mast cells, because the former did not respond to morphine [12]. There is increasing evidence that cardiac mast cells participate in the development of atherosclerosis, coronary inflammation, and cardiac ischemia [13], as well as the metabolic syndrome [14]. Although the mechanisms by which mast cells participate are not fully understood, the implications are exciting and suggest the potential use of mast cell inhibitors for the management of these diseases. Here, we review key evidence that mast cells participate in coronary artery disease (CAD) and obesity through local release of numerous pro-inflammatory and tissue remodeling mediators.

Atherosclerosis

Atherosclerosis is a disease of the inner layer of the arterial wall, the intima. It is characterized by smooth muscle cell (SMC) migration and proliferation, lipid deposition, inflammatory cell infiltration and matrix degradation. Accumulation of blood-derived lipoprotein lipids, notably cholesterol, eventually leads to development of atherosclerotic plaques. Acute coronary syndromes are most commonly (75%) caused by the rupture of atherosclerotic plaques [15], especially thin-cap fibro-atheromas, leading to an occluding thrombus of a coronary artery; they manifest clinically as unstable angina or acute myocardial infarction (MI). Acute coronary thromboses are can also be caused by superficial erosion of the coronary plaque. Increasing evidence indicates that atherosclerosis involves inflammation not only of the intima, but also of the arterial adventitia, which may be more important than simple cholesterol accumulation because the inflammatory plaque is likely to break off and cause infarcts [15–17].

Increased serum levels of C-reactive protein (CRP) [18] and interleukin (IL)-6 [18], especially intracardiac IL-6 [19], have been reported as independent risk factors for cardiovascular disease. High plaque levels of CRP and IL-6

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were significantly related to increased risk of CAD [20]. IL-1 expressed from secondary inflammatory plaques could also stimulate mast cells to release IL-6 [21].

Mast cells have been identified in coronary arteries during spasm [22], accumulate in the rupture prone shoulder region of coronary atheromas [13,23] (Figure 1), and are associated specifically with plaque rupture [23,24]. More importantly, mast cell numbers are correlated with the incidence of plaque rupture and erosion [25]. Degranulated mast cells were identified in the adventitia of vulnerable and ruptured lesions in patients with MI [25].

Mast cells may also be involved in many cases of CAD that develop in the absence of atherosclerosis. Such cases could be associated with coronary hypersensitivity, known as Kounis syndrome [26], or are precipitated by acute stress [27]. Mast cells could be stimulated by corticotropin-releasing hormone (CRH), secreted under stress, to release vascular endothelial growth factor (VEGF) [28]. The CRH-related peptide urocortin has also been reported to stimulate IL-6 release from neonatal cardiomyocytes [29].

Cardiovascular mast cell stimulation

The triggers responsible for initiating activation of cardiac mast cells in CAD are poorly understood (Figure 1). Of particular interest is the observation that lipoproteins, specifically oxidized low density lipoprotein (LDL), can activate mast cells [30]. The complement fragment C5a is a known chemotactic factor for mast cells and is also important in ruptured coronary plaque scar formation in MI [31]. Such triggers do not appear to induce anaphylaxis, and may secrete specific mediators selectively without degranulation [32], as previously shown for IL-1 [21] and CRH [28].

An important vascular wall-related mast cell-specific trigger is endothelin-1 (ET-1), a 21 amino acid peptide with mitogenic and vasoconstrictive properties that accounts for most of the resting tone in atherosclerotic coronary arteries. Circulating ET-1 is increased in patients with atherosclerosis and coronary endothelial dysfunction [33]. Long term administration of ET-1 receptor antagonists improves coronary endothelial function in patients with early atherosclerosis [34]. Administration of ET-1 to blood-perfused, isolated rat hearts resulted in extensive mast cell degranulation, increased matrix metalloproteinase 2 (MMP-2) activity and collagen degradation [35]. When stimulated, mast cells induce increased expression of ET-1 mRNA in cultured endothelial cells, but also increase degradation of the ET-1 peptide through mast cell proteases [36].

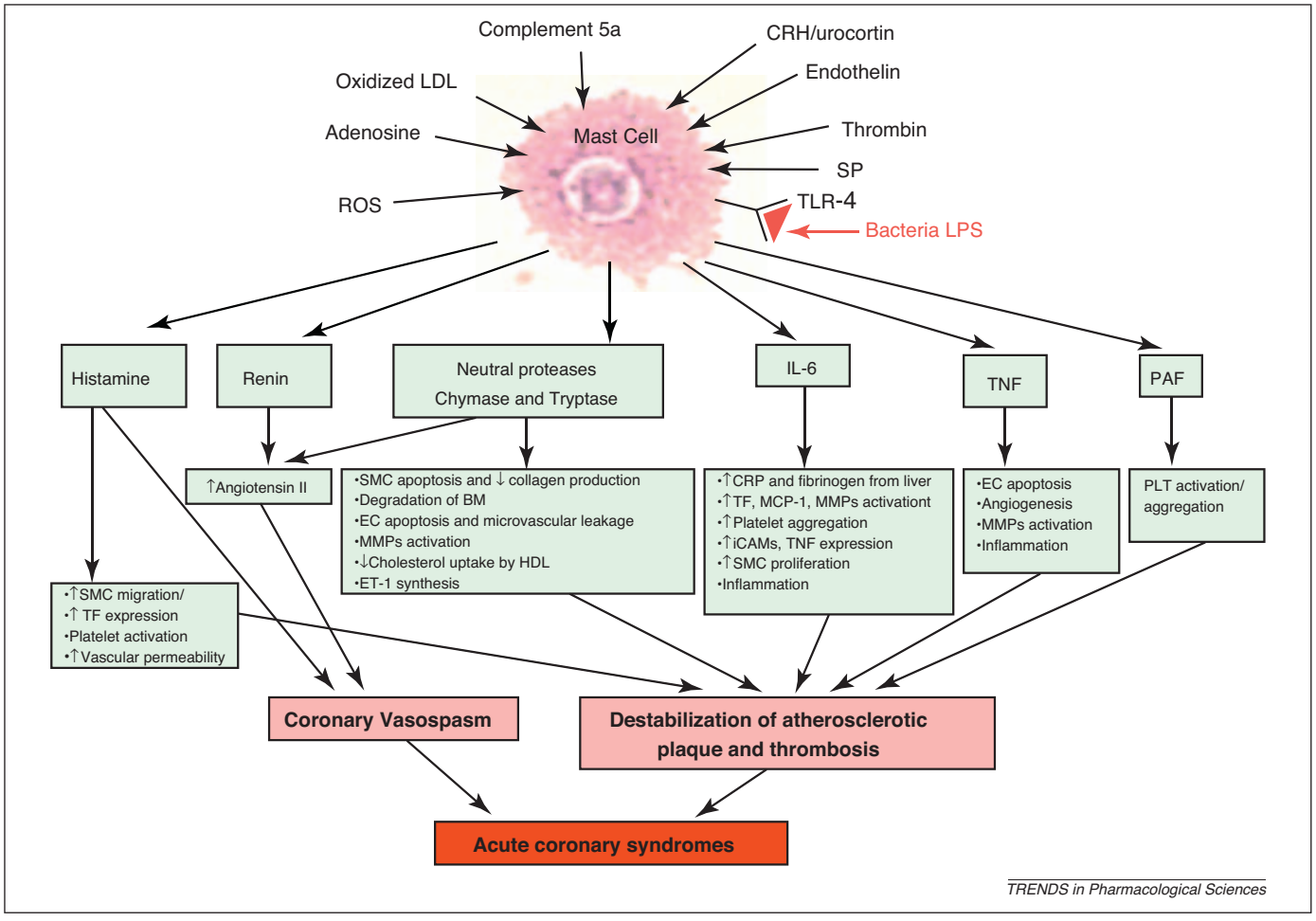

Figure 1. Possible trigger of cardiovascular mast cells and their key mediators with coronary artery disease (CAD)-relevant actions and major pathological sequelae. Various activators of mast cells trigger their degranulation and the release of compounds that contribute to inflammation and other processes involved in the destabilization of atherosclerotic plaques. Release of histamine and renin from mast cells can trigger coronary vasospasm, another type of acute coronary syndrome. LDL, low density lipoprotein; ROS, reduced oxygen species; SP, substance P; IL-6, interleukin-6; TNF, tumor necrosis factor; PAF, platelet activating factor; SMC, smooth muscle cell; BM, basement membrane; EC, endothelial cell; MMP, matrix metalloproteinase; ET-1, endothelin-1; CRP, C-reactive protein; TF, tissue factor; MCP-1, monocyte chemotactic protein-1; iCAM, intercellular adhesion molecule; PLT, platelet.

Oxidative stress and inflammation play an important role in cardiac tissue damage when blood supply returns after a period of ischemia, a phenomenon known as ischemia reperfusion (I/R) injury. Release of tumor necrosis factor (TNF) during myocardial I/R depends on oxidative stress and is prevented by mast cell stabilizers, and the superoxide dismutase mimetic M-40403 has been reported to prevent mast cell degranulation following reperfusion of ischemic rat heart [37]. Reactive oxygen species (ROS) can also activate mast cells [38]. Mitochondrial uncoupling protein 2, which is known to regulate ROS production, was recently reported to inhibit mast cell activation [39].

ROS induce the release of substance P (SP) from sensory nerves during I/R [40]. Stimulation of these cardiac sensory c-fibers results in SP secretion and mast cell degranulation with renin release that activates the renin–angiotensin system, causing sustained reperfusion arrhythmias [41]; SP receptor blockage prevented these changes [41]. Adventitial mast cells are localized close to nerve endings in atherosclerotic coronary arteries and correlate with the number of nerve fibers [42]. Moreover, SP treatment significantly increased the number and extent of degranulation of adventitial mast cells compared to controls, and promoted intraplaque hemorrhage; these effects could be prevented by coadministration of the neurokinin-1 receptor antagonist Spantide I and did not occur in mast cell deficient ApoE$^{-/-}$ mice [42]. These mice are deficient in apolipoprotein E (ApoE), leading to hyperlipidemia and development of spontaneous atherosclerosis. In addition to stimulating the secretion of histamine and other inflammatory mediators, SP could induce mast cells to release VEGF, an action augmented by IL-33 [43]. Nerve fibers immunoreactive for neurotensin (NT) are also present in the heart, and NT can lead to coronary vasoconstriction [44]. A synergistic role of CRH and NT was reported for acute stress-induced mast cell degranulation with an increase in vascular permeability [45], possibly through release of VEGF [28]. An NT-receptor antagonist blocked stress-induced cardiac mast cell degranulation [46].

Infectious agents such as *Chlamydia pneumonia* and *Porphyromonas gingivalis* have been detected in atherosclerosis and could activate toll-like receptors (TLRs), which can affect atherogenesis [47]. Downstream signalling of these receptors can elicit pro-inflammatory cytokine release, lipid uptake, foam cell formation, and activation of the cells of the adaptive immune system. Expression of both TLR2 and TLR4 is increased in LDLr$^{-/-}$ and ApoE$^{-/-}$ mice [48]. LDLr$^{-/-}$ mice are deficient in LDL receptor, leading to hypercholesterolemia and the development of spontaneous atherosclerosis. Mast cells express most TLRs [49]. There is increasing evidence that TLR signaling may also be elicited in the absence of infection through 'endogenous' ligands generated at sites of tissue remodeling and inflammation. We recently reported that mast cell activation results in mitochondrial translocation to the cell surface [50], and extracellular release of DNA that acts as an 'innate pathogen' [4].

Cardiovascular mast cell mediators

Several mast cell-derived mediators can affect cardiovascular function and contribute to CAD. The development of mast cell deficient mice has contributed greatly to the understanding of their role in inflammatory processes. These mice lack the c-kit receptor for SCF, precluding the development of functional mast cells even though they have normal precursors. There are two types of mast cell deficient mice, W/W^{v} and kit$^{w\text{-}sh/w\text{-}sh}$; both are albino because melanocyte development requires intact c-kit, but their other immune functions are apparently intact [51]. Acute stress caused a greater increase in serum IL-6 in ApoE$^{-/-}$, atherosclerosis-prone mice [52], an effect that was absent in W/W^{v} mast cell deficient mice and partially inhibited by disodium cromoglycate (cromolyn), a rodent mast cell stabilizer [52]. Serum IL-6 was increased in I/R in mice and its levels correlated with the extent of cardiac tissue necrosis [53]; by contrast, mast cell deficient mice had normal IL-6 levels and less cardiac tissue necrosis [53]. Human coronary artery specimens also contain mast cells that store and release TNF [24]. Indeed, mast cells are the only 'immune cells' that store preformed TNF in their secretory granules [54]. Mast cell-derived TNF-α contributes to the upregulation of IL-6 in infiltrating leukocytes and initiates the cytokine cascade responsible for myocyte intercellular adhesion molecule-1 (ICAM-1) induction and subsequent neutrophil-induced injury [55].

Atheroma size and lipid deposition were reduced in mast cell deficient LDLr$^{-/-}$ mice and they had fewer T cells and macrophages than atherosclerosis-prone LDLr$^{-/-}$ mice [56]. Adoptive transfer of bone marrow-derived mast cell precursors from normal wild-type mice to LDLr$^{-/-}$ kit$^{w\text{-}sh/w\text{-}sh}$ mice restored atherogenesis; however, when IL-6 and interferon-gamma (IFN-γ) deficient mast cells were reconstituted, the atherogenesis failed to occur [56]. Mast cell deficient kit$^{w\text{-}sh/w\text{-}sh}$ mice had significantly lower serum cholesterol and triglyceride levels, with a concomitant decrease in atherogenic apoB-containing particles and serum pre-high density lipoprotein (HDL) and phospholipid transfer protein activity [57]. Serum soluble intercellular adhesion molecules were also decreased in these mast cell deficient mice [57]

Mast cells and basophils are the richest source of histamine. Blood histamine levels are associated with CAD, severity of inflammation and atherosclerosis [58]. Histamine constricts the coronary arteries and can induce coronary spasm, increases vascular permeability and promotes inflammation. Histamine also has pro-arrhythmogenic properties, and induces SMC migration and proliferation, as well as intimal thickening. It also induces endothelial cell release of IL-6 and IL-8, production of which is increased by lipopolysaccharide and TNF-α,, which can also contribute to endothelial apoptosis [59].

Cardiac mast cells contain renin, which they secrete during I/R, thereby initiating local angiotensin formation [60]. Moreover, the human mast cell proteolytic enzyme chymase has been shown to be the main cardiac source of converting enzyme, generating the well known coronary constrictor angiotensin II [61], which also causes arrhythmias [60], endothelin release, and SMC and cardiomyocyte apoptosis. Mast cell chymase activates pro-MMP-1, and human mast cells also secrete MMP-9 on contact with activated T cells through the activation of TNF-α [62]. Chymase, tryptase, and cathepsin G can degrade vascular

endothelial cadherin, a molecule involved in the survival signaling of endothelial cells and plaque erosion [63]. Tryptase further leads to inflammation through protease activated receptors, which are stimulated by thrombin on mast cells [64].

Mast cells produce arachidonic acid metabolites. The 5-lipoxygenase (5-LO) cascade leads to formation of leukotrienes, which exhibit strong pro-inflammatory activity in cardiovascular tissues [65]. Expression of the 5-LO pathway is increased in the arterial walls of patients with various stages of atherosclerosis, and mast cells in atherosclerotic plaques are positive for 5-LO [66]. Deficiency of one 5-LO allele conferred potent protection against the development of atherosclerosis in $LDLr^{-/-}$ mice, and leukotriene B_4 receptor antagonism was also protective in three atherosclerosis susceptible mouse strains [66].

Mast cell-derived IL-8, monocyte chemotactic protein-1 and regulated upon activation, normal T cell expressed, and secreted (RANTES) could recruit macrophages and mast cells to the affected coronary arteries, thereby worsening the problem.

Obesity and diabetes

The increase in the prevalence of obesity and its strong association with insulin resistance and type 2 diabetes have recently also been linked to inflammation. [67–70]. There are two types of adipose tissue that have essentially antagonistic functions: WAT, which regulates energy balance [71], and brown adipose tissue (BAT), which affects sensitivity to insulin and susceptibility to weight gain [72]. During the past few years, adipocytes in WAT have been implicated in the production of adipocytokines [73] such as IL-6 [74], chronic inflammation, and adiponectin and leptin secretion as well as insulin resistance [73].

Adipocytokines have also been associated with allergic inflammation and mast cells [75]. Lipoproteins [30] and advanced glycation end products that accumulate in diabetes and obesity can activate mast cells [76]. Macrophages [77] and T cells [78] are also increased in obese WAT compared to lean tissue. Saturated fatty acids can stimulate TLRs [79], leading to activation of the inflammasome and release of IL-1 [80]. Genetic loss of TLR4 can ameliorate insulin resistance [81].

WAT from obese humans and mice contains more mast cells (Figure 2) than WAT from their lean counterparts [82]. $kit^{w\text{-}sh/w\text{-}sh}$ mast cell deficient mice fed a Western-patterned diet (high in fat and sugar) for 12 weeks gained significantly less body weight than wild-type congenic controls; in addition, serum and WAT levels of inflammatory cytokines, chemokines, and proteases were reduced as glucose homeostasis and energy expenditure improved [82]. Adoptive transfer of bone marrow-derived mast cell progenitors from different cytokine deficient mice into $kit^{w\text{-}sh/w\text{-}sh}$ mast cell deficient mice demonstrated that mast cells contributed to diet-induced obesity by producing inflammatory cytokines such as IL-6 and IFN-γ [82]. $kit^{w\text{-}sh/w\text{-}sh}$ mice that received bone marrow-derived progenitors from $IL\text{-}6^{-/-}$ mice and $IFN\text{-}\gamma^{-/-}$ mice showed less body weight gain and improved glucose tolerance [82]. Other studies have shown that TNF-α is overexpressed in WAT from obese subjects and mediates insulin resistance by targeting insulin receptor substrate 1 [83]. Lack of TNF-α ligand or the p55 TNF receptor improves insulin sensitivity and glucose homeostasis, suggesting that this

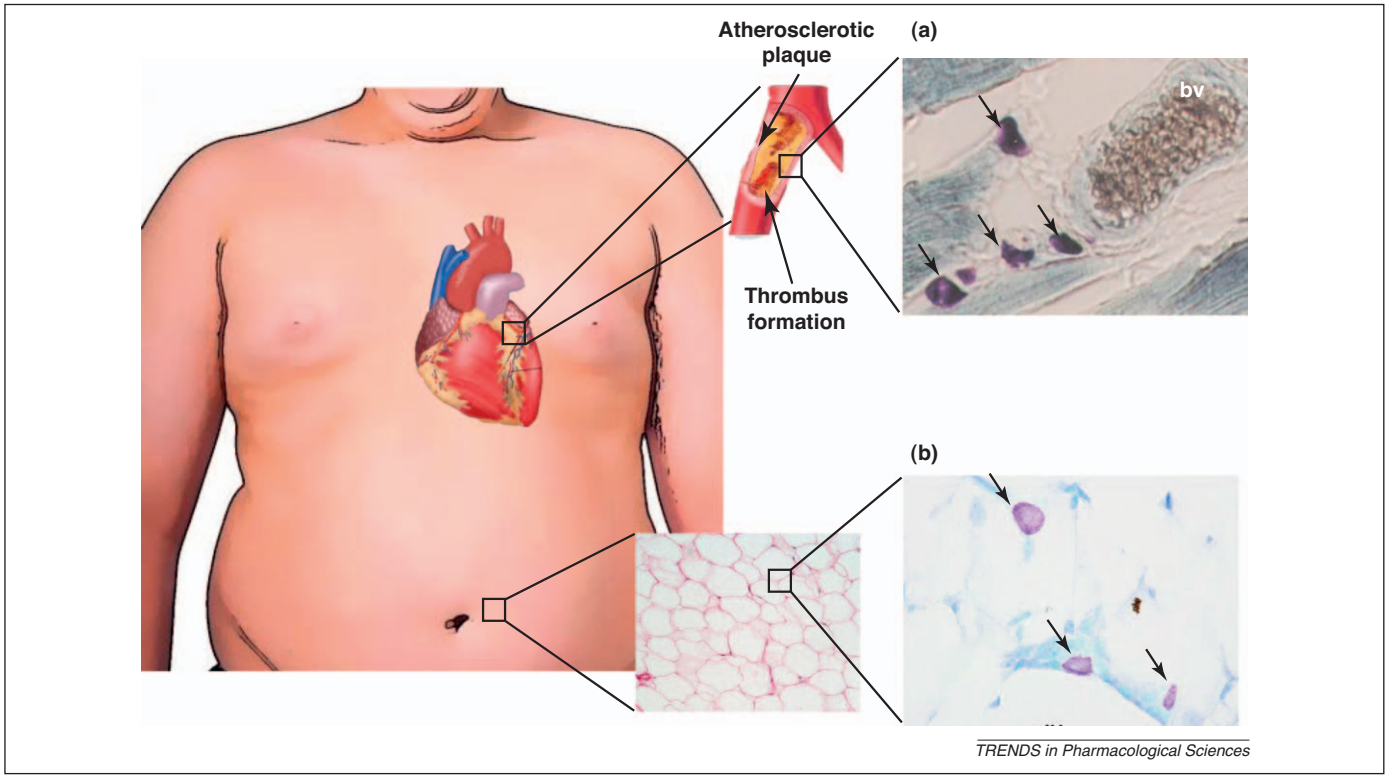

Figure 2. Mast cells stained with toluidine blue (arrows) (**a**) close to coronary blood vessel (bv), occluded by lipid deposits stained with Sudan black; (**b**) among adipocytes in white adipose tissue.

inflammatory response is important in the regulation of insulin action in obesity [84].

$kit^{w\text{-}sh/w\text{-}sh}$ mice and those receiving cromolyn also exhibited significantly lower concentrations of serum leptin than wild-type controls [82]. Leptin is a cytokine-like hormone, secreted principally by adipocytes, that regulates body weight and food intake but also has beneficial actions in metabolic and immune functions [85]. Human mast cells express both leptin and leptin receptors [86]. Mast cells are mostly localized next to microvessels in WAT and may contribute to obesity by promoting angiogenesis (Figure 1). Microvessels not only promote WAT tissue increase, but also permit macrophage infiltration, followed by adipocytokine release and further angiogenesis and WAT involvement in obesity [87]. It is interesting that inhibition of angiogenesis blocked adipose tissue development in mice [88].

Obesity is a major risk factor for insulin resistance and type 2 diabetes. How obesity promotes insulin resistance remains unclear, but the inflammatory response is thought to be a potentially important mechanism that could alter adipose tissue function, leading to systemic insulin resistance [70]. Adipocytes are the only cells that release adiponectin, associated with insulin resistance, and patients with type 2 diabetes are reported to have decreased circulating adiponectin. [89]. CRH regulates adipocyte metabolism, and both CRH receptor 1 (CRH-R1) and CRH-R2 are expressed by human adipocytes [90]. These results indicate that CRH may regulate adipocyte function both directly and through adipocyte-associated mast cells [91].

Treatment approaches

Therapeutic interventions through inhibition of inflammatory pathways appear promising in CAD and obesity [92,93]. A recent study showed that treatment of obese type 2 diabetics with etanercept, a TNF-α antagonist, resulted in improved glycemia and increased adiponectin levels [94]. Thiazolidienes, which are potent agonists of peroxisome proliferator-activated receptor gamma (PPARγ), can restore lipogenic function to adipocytes and also possess anti-inflammatory properties [95,96]. The beneficial effect of acetyl salicylic acid in CAD and diabetes also may result not from its anti-clotting but from its anti-inflammatory effect [97]. Moreover, recent evidence indicates that statins also have anti-inflammatory actions [98].

Given the findings discussed above, with respect to the potential mechanisms through which mast cells could contribute to CAD (Table 1) and obesity, it would be desirable to block mast cells. Unfortunately, there is no effective human mast cell inhibitor available (Table 2). Although cromolyn inhibits histamine secretion from rodent mast cells, it is a very weak inhibitor of human mast cells [99]. The histamine-1 receptor antagonist ketotifen, which also partially inhibits mast cells, is available only for allergic conjunctivitis in the USA. Some of the non-sedating histamine-1 receptor antagonists, such as azelastine, partially inhibit the release of mediators from human mast cells [100]. The newest histamine-1 receptor antagonist, rupatadine (not available in the USA), which blocks the action of platelet activating factor and has anti-eosinophilic properties, also exhibits mast cell inhibitory actions [101]. Histamine-3 receptor agonists are auto-inhibitory on mast cells and have been considered as potential treatments for CAD [102]

Several chymase inhibitors are being developed, but are not clinically available [103]. At least one tryptase inhibitor, APC 2059, has been tested for asthma [104] and could be used for CAD-related indications.

Niacin is well known for its ability to reduce total cholesterol and LDL, while increasing HDL [105]. Recent evidence indicates that niacin may also prevent the release of inflammatory mediators from adipocytes [105]. However, niacin causes intense flush, even in slow or extended release forms [106], which limits compliance. A new

Table 1. Mechanisms through which mast cells contribute to the pathogenesis of coronary artery disease

Mediator	Effect
Histamine	Coronary constriction (through action on smooth muscle cells [SMCs]), ↑ vascular permeability (through action on endothelial cells), intima thickening, P-selectin upregulation, inflammatory cell modulation, upregulation of tissue factor expression, sensitization of nerve endings in plaques, potentiation of the aggregating response to platelet activating factor (PAF), serotonin and thrombin
Interleukin (IL)-6	↑ C-reactive protein, promotes inflammation, restenosis, and neutrophil recruitment
IL-8	Promotes neutrophil recruitment, neovascularization
Tryptase and chymase	Promote inflammation, activate matrix metalloproteinases (MMPs), promote foam cell formation, degradation of endothelium basement membrane, microvascular leakage, high density lipoprotein (HDL) degradation
Tryptase	Protease activated recepter-2 and thrombin receptor activation, HDL degradation
Chymase	Angiotensin II synthesis, SMC apoptosis and decreased collagen synthesis, endothelin synthesis, endothelial cell apoptosis
Growth factors (vascular endothelial growth factor, transforming growth factor beta, nerve growth factor, fibroblast)	Neovascularization leading to intraplaque hemorrhage and ↑ vascular permeability, inflammation
MMP-9	Matrix degradation
PAF	Activates platelets and promotes platelet aggregation, leukocyte activation
Tumor necrosis factor alpha	Promotes inflammation, endothelial cell apoptosis, activation of MMPs
Renin	Angiotensin synthesis
Leukotrienes	Vasoconstriction
Thromboxane	Vasoconstriction, platelet aggregation

Table 2. Compounds affecting mast cell functions

Class and compound	Mast cell action	Potency	Use
Phenols			
Cromolyn	↓ Histamine secretion*	+	Allergic conjunctivitis Food allergy
Ledoxamine	↓ Histamine secretion	+	Allergic conjunctivitis
Luteolin	↓ Histamine and cytokine secretion	+++	Dietary supplement
Quercetin	↓ Histamine and cytokine secretion	+ + +	Dietary supplement
Antihistamines			
Azelastine	↓ Histamine and cytokine secretion	+	Allergic conjunctivitis
Desloratadine	↓ Histamine and cytokine secretion	+	Allergies, pruritus
Hydroxyzine	↓ Histamine and cytokine secretion	+	Allergies, mast cell inhibition
Ketotifen	↓ Histamine and cytokine secretion	++	Allergies, pruritus
Rupatadine	↓ Histamine and cytokine secretion	+++	Allergies, pruritus, mast cell inhibition
Enzyme inhibitors			
α-1 Antitrypsin	Mast cell inhibition		?
Anti-IgE	Mast cell inhibition		Asthma
Chymase inhibitors (e.g. APC 2059, APC 366)	Mast cell stabilization, ↓ lipid deposition, ↓ local renin–angiotensin system activation		?

*Potent inhibition in rodents but not in humans.

Table 3. Unique benefits of CardioNiacin®*

Component	Actions	Side effects	References
Niacin, extended release	↓ cholesterol, ↓LDL, ↑HDL, ↓ adipocytokines	Flush	[105,106]
Luteolin	↓ Inflammation, ↓ flush, ↓ mast cell activation, ↓ adipocyte-dependent macrophage activation, improves endothelial insulin sensitivity	N/A	[107–109,111,113]
Luteolin-glycoside	↓ Cholesterol, ↓LDL	N/A	[112]
Quercetin†	↓ Inflammation, ↓ flush, ↓ mast cell activation, ↓ CRP, ↓ IL-6, ↓ PGD_2, mimics GLP-1 actions	N/A	[111,115]
Olive kernel oil	↓ Cholesterol, ↓ LDL, ↑ absorption of flavonoids	N/A	

LDL, low density lipoprotein; HDL, high density lipoprotein; CRP, C-reactive protein; IL-6, interleukin-6; PGD_2, prostaglandin D2; GLP-1, glucagon-like peptide-1.

*Covered by US Patent Nos. 6,624,148, 7,115,278, 7,759,307, and 11/999,991

†Water soluble (patent pending).

dietary supplement (Table 3), formulated in olive kernel oil to increase absorption of the active ingredients and provide the well known 'Mediterranean diet' effect, contains extended release niacin together with the naturally occurring flavonoids luteolin and quercetin, which prevent niacin-induced flush [107–109]. Luteolin and quercetin exhibit potent antioxidant and anti-inflammatory [110] as well as mast cell inhibitory [**111**] actions, and inhibit mast cell release of IL-6 and PGD_2 [21]. In addition, 7-luteolin-glycoside has an independent ability to reduce total cholesterol [112]. Luteolin suppresses adipocyte activation of macrophages and also inhibits inflammation and increases the insulin sensitivity of the endothelium [113,114]. Quercetin mimics the action of glucagon-like peptide-1, a promising target for type 2 diabetes [115]. As yet, there is only anecdotal evidence of positive effects. However, a pilot clinical trial of this formulation is under way, with a larger double-blind study planned for the near future.

Recently, a clinical study comparing simvastatin alone to simvastatin plus extended release niacin (Niaspan) was halted prematurely because of no apparent reduction in cardiovascular events, and a possible increase in strokes after the study was halted [116,117]. However, this study used subjects already controlled on statins, did not figure in the adverse effect of niacin-induced flush, and did not investigate the contribution of inflammatory markers. Moreover, contrary to the preliminary findings that led to the discontinuation of this study, a recent meta-analysis indicated a reduction in cardiovascular events among those taking niacin, possibly with the exception of strokes [118]. In addition, animal studies have shown that niacin can actually prevent strokes [119,120]. Further research will be needed to clarify the differences among these findings.

Concluding remarks

Diverse evidence indicates that inflammation contributes greatly to CAD, obesity, and the metabolic syndrome. Increasing evidence now implicates mast cells in inflammatory diseases through activation by non-allergic triggers such as neuropeptides and cytokines. Targeting mast cells and their downstream effects might be beneficial for the treatment of CAD and obesity. A multimodal treatment might be the best approach for these diseases, with formulations that combine anti-inflammatory agents, such as select flavonoids, with niacin.

Disclosures

T.C.T. is the recipient of US Patents No. 5,821,259, 6,624,148, 7,115,278, 7,759,307, and 11/999,991 covering the use of flavonoids and histamine 3-agonists in the treatment of CAD and in reducing niacin-induced flush.

He is also the inventor of the niacin/luteolin-containing formulation CardioNiacin®, with US Trademark No. 8,5119,878. All patents and the trademark have been assigned to Theta Biomedical Consulting and Development Co., Inc. (Brookline, MA) and some have been licensed to Thorne Research, (Sandpoint, ID).

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