Mast Cells as Effectors in Atherosclerosis

Ilze Bot, Guo-Ping Shi, Petri T. Kovanen

Abstract—The mast cell is a potent immune cell known for its functions in host defense responses and diseases, such as asthma and allergies. In the past years, accumulating evidence established the contribution of the mast cell to cardiovascular diseases as well, in particular, by its effects on atherosclerotic plaque progression and destabilization. Through its release not only of mediators, such as the mast cell–specific proteases chymase and tryptase, but also of growth factors, histamine, and chemokines, activated mast cells can have detrimental effects on its immediate surroundings in the vessel wall. This results in matrix degradation, apoptosis, and enhanced recruitment of inflammatory cells, thereby actively contributing to cardiovascular diseases. In this review, we will discuss the current knowledge on mast cell function in cardiovascular diseases and speculate on potential novel therapeutic strategies to prevent acute cardiovascular syndromes via targeting of mast cells. (Arterioscler Thromb Vasc Biol 2014;35:00-00.)

Key Words: atherosclerosis ■ leukocytes ■ mast cells

Acute cardiovascular syndromes (ACS) remain one of the leading causes of death in Western societies, and the main cardiovascular disorder causing these acute cardiovascular events is the development of atherosclerosis. Lipid accumulation, matrix degradation, and infiltration of several different proinflammatory immune cells are considered key mechanisms in the development of atherosclerosis and the pathogenesis of plaque rupture, and intervention strategies are aimed at halting these processes. A novel therapeutic target may be the mast cell, the number of which has been shown to increase within the arterial wall during atherosclerotic plaque progression.

The mast cell, a highly potent immune cell, was first described by Ehrlich in 1876, who called it Mastzelle (the German word meaning suckling) in the belief that they had taken up nutrients and stored them in their cytoplasmic storage granules. Mästung denoting suckling) in the belief that they had taken up nutrients and stored them in their cytoplasmic storage granules. Mast cells originate from hematopoietic stem cells in the bone marrow and are derived from progenitor cells that circulate in the blood. Once recruited into tissues, mast cell progenitors mature into either a connective tissue type or a mucosal type of mast cell, depending on specific stimuli within the tissues. The granule neutral proteases are the most precise markers of phenotypic heterogeneity and plasticity of mast cells in tissues. Thus, all human mast cells contain the mast cell–specific protease tryptase, and a fraction of them also contains chymase and other granule proteases. Like in other tissues, also in the vessel wall, all mast cells contain tryptase, whereas a highly variable fraction of them also contains chymase, illustrative of the presence of different subclasses of mast cells in the vasculature and of the strong variation in the relative proportion of the chymase-containing mast cells among individuals. Increased mast cell numbers have been detected during the progression of atherosclerosis, and, in particular, in ruptured human coronary plaques, as well as in the backing adventitial tissue, where the distribution density of mast cells was demonstrated to be high. These findings have fueled the hypothesis that mast cells, by their activation and immediate release of their contents, may actively contribute to atherosclerotic plaque progression and destabilization, leading to plaque rupture or erosion. In the past few years, research has focused on the questions whether and how mast cells are directly involved in atherosclerosis and ACS. In this short review, we will focus on the current evidence describing the contribution of mast cells to atherosclerosis.

Mast Cells in Atherosclerosis

In the 1990s, mast cells were described to accumulate in the human arterial intima and adventitia during atherosclerotic plaque progression, and at that time, it was already postulated that mast cells actively participate in plaque destabilization. Mast cells were hypothesized to be recruited to the atherosclerotic plaque via the chemokine eotaxin (CCL11) expressed in the plaque and by its receptor CCR3 on the mast cell. Interference in CCR3 signaling using a CCR3 antagonist in apoE-deficient mice resulted in reduced mast cell recruitment to the adventitial tissue, thereby inhibiting plaque progression. Little is known about other mechanisms directly involved in the recruitment of mast cell progenitors to the adventitia or atherosclerotic plaque; however, one can envision that additional chemokines, such as CXCL1, or factors such as stem cell factor may be involved in mast cell recruitment to the adventitia or plaque itself and thus may be of therapeutic interest for the prevention of plaque progression.

Mast cells within the plaque were found to be located near plaque microvessels and were demonstrated to contain the basic fibroblast growth factor. It was thus suggested that mast...
cells, by virtue of their capability to release angiogenic compounds, histamine, and pericellular matrix-degrading proteases, induce not only growth of microvessels but also leakiness and rupture of the fragile neovessels, which results in intraplaque hemorrhage. Interestingly, it was recently established that mast cell numbers in plaques of patients who underwent a carotid endarterectomy correlate not only with plaque progression but also with intraplaque microvessel density. In this study, mast cell numbers directly correlated with the incidence of intraplaque hemorrhage, and strikingly, were also found to associate with the incidence of future cardiovascular events, suggesting a causal relationship between mast cell number in the plaque and disease outcome. Direct experimental proof for instrumental effects of the mast cell to atherosclerosis was first reported in 2007, when 2 experimental studies independently provided evidence of a causal relationship between mast cells and atherosclerosis. In the first study, mast cell activation during progression of atherosclerosis was seen to increase lesion size in the brachiocephalic artery of apoE-deficient mice, while also enhancing the incidence of intraplaque hemorrhage in collar-induced carotid artery lesions. Interestingly, the mast cell stabilizer cromolyn prevented these adverse effects, which provided further proof of mast cell dependency. In the second study, genetic mast cell deficiency inhibited plaque development in low-density lipoprotein receptor (LDLR)–deficient mice, which could be restored by repopulation with bone marrow–derived mast cells. In fact, in this study, mast cell–derived interferon γ and interleukin-6 were identified as culprit actors in mast cell–mediated plaque progression. Moreover, the mast cell–deficient LDLR F KIT(W T1/2) mouse was used to investigate the effects of mast cells on lipid metabolism and atherosclerosis. Interestingly, lack of mast cells was associated with a decrease in lesion size, which was described to be partly caused by reduced serum total cholesterol and triglyceride levels, and partly because of a reduction in vascular inflammation. In line with these findings, activation of mast cells by the commonly used mast cell activator compound 48/80 induced atherogenic lesion development, whereas treatment with cromolyn inhibited compound 48/80–induced mast cell activation and plaque progression.

The above described in vivo studies all identify mast cells as proatherogenic. It must be noted that in mice, mast cells mainly reside in the perivascular tissue and are rather scarce in the intima, whereas in patients with cardiovascular diseases, mast cells accumulate both in the intimal and in the adventitial tissue. Mast cell–mediated effects observed in mouse models of atherosclerosis may thus not completely reflect human pathology and may even not be as potent, and even underestimated, when compared with human atherosclerosis where intimal effects may be more prominent. For example, because mast cells in human plaques particularly cluster around neovessels, mast cell–induced vascular leakage and the concomitant increased incidence of intraplaque hemorrhage may be more evident in human lesions when compared with mouse plaque. Although the data obtained from mouse studies already provide convincing evidence of a proatherogenic role for mast cells in atherosclerosis, mast cell activation in other atherosclerotic animal models, in which mast cells accumulate in intimal tissue, may lead to the elucidation of even more specific mechanisms in mast cell–induced plaque progression and destabilization.

As discussed in the section above, observations in human pathology and results from studies in experimental animals associate mast cells with the development and progression of atherosclerosis. However, other diseases exist in which mast cells play a central pathophysiological role, such as in mastocytosis, allergic asthma, and hyper-IgE syndrome. However, a limited number of studies have linked these diseases to cardiovascular diseases. For example, in mastocytosis, where patients have excessive amounts of mast cells in tissues, anaphylactic shock is the most predominant cause of hospitalization or sudden death. Cardiac mast cell activation during such an extreme mast cell degranulation phase can, however, lead to build-up of cardiotoxic mast cell mediators within the cardiac tissue, thereby damaging the heart. Preexisting coronary atherosclerosis may further favor ischemia in the heart tissue leading to myocardial infarction (as reviewed by Mueller29). Because these patients already have increased plasma tryptase levels, the development of atherosclerosis in these patients may be enhanced, but additional studies need to confirm this hypothesis. Hyper-IgE syndrome is a rare immunodeficiency disorder resulting predominantly from STAT3 mutations and is characterized by increased circulating IgE levels. Strikingly, these patients frequently have coronary artery anomalies, notably aneurysms, whereas coronary atherosclerosis is rarely observed in this population. Direct experimental proof providing an association between the occurrence of allergic asthma or allergies and atherosclerosis via the mast cell has up to date not been delivered.

Taken together, the histological observations in human atherosclerotic samples and the described experimental studies in mice (Table 1) provide evidence that mast cells are more than just bystanders in the process of atherosclerosis, and that there are multiple mechanisms by which these cells contribute to the progression of this disease. Below we will summarize the current knowledge on mast cell–mediated processes in plaque progression and destabilization.

**Mast Cell Effector Mechanisms**

Mast cells contain a plethora of different mediators, which endow them the capacity to exert several effector mechanisms. However, for the mast cells to act as effector cells and to induce plaque progression, they need to be activated to release their mediators. One of the primary plaque destabilizing effects is thought to be mediated by the mast cell–specific proteases tryptase and chymase. In several studies, plasma tryptase levels have been shown to correlate with the severity of cardiovascular diseases and interestingly, plasma tryptase levels were significantly higher in patients who had a secondary cardiovascular event after carotid endarterectomy, thus being a marker with certain predictive value in cardiovascular diseases. However, because other studies failed to show any increase in systemic tryptase levels during cardiovascular events, tryptase effects may be more evident locally within the culprit lesion without any measurable release of tryptase into the systemic environment.
Angina pectoris.33 Chymase can contribute to atherosclerosis by its ability to modify high-density lipoprotein, thereby affecting its cholesterol efflux ability,40,41 whereas also enhancing the formation of angiotensin II, a potent proatherogenic factor.42 Furthermore, chymase was established to induce apoptosis of vascular smooth muscle cells43,44 and endothelial cells,45,46 rendering the atherosclerotic plaque more prone to rupture or erosion. Inhibition of chymase was seen to inhibit experimental atherosclerosis in hamsters47 and was shown to reduce the incidence and size of intraplaque hemorrhage in carotid artery atherosclerosis in apoE−/− mice.48 Interference in mast cell function by the use of the mast cell stabilizer tranilast inhibited plaque formation in a hamster model of atherosclerosis, which was attributed to be caused by an inhibition of chymase.49 However, one must take into account that tranilast, which is generally known as a mast cell–stabilizing and anti-inflammatory drug, does not specifically inhibit mast cell chymase.50 Finally, tryptase and chymase were seen to activate matrix-degrading metalloproteinases,51 providing another mechanism of plaque destabilization by mast cell–specific proteases.

In line with a proatherogenic role for mast cells, mast cell activation has also been shown to enhance lipid uptake by macrophages. Heparin secreted from mast cells can bind LDL particles, and the formed complexes are subsequently phagocytosed by macrophages, resulting in foam cell formation, both in vitro and in vivo.52–55 Furthermore, mast cells can affect the stability of the atherosclerotic plaque via the recruitment of new inflammatory cells. Indeed, local mast cell activation in the arterial wall induces leukocyte recruitment and adhesion, which could be prevented by antibodies against CXCR2 and VLA-4.21 This may be directly caused by chemokine release from the mast cell, for example, by release of interleukin-8, because mast cell activation in the peritoneal cavity resulted in an acute influx of CXCR2+ neutrophils in C57Bl6 mice, which did not occur upon mast cell activation in apoE−/− mice.56 However, mast cell–dependent leukocyte recruitment can also be mediated via upregulation of adhesion molecules on the endothelial cells.57 Furthermore, microvascular leakage induced by mast cell histamine contributes not only to the increase in intraplaque erythrocytes but also to enhanced inflammatory cells within the plaque.

A distinction can be made on mast cell–mediated effects on plaque development and progression and acute effects of mast cell activation on advanced plaques. A continuous, systemic increase in mast cell activation during plaque development leads to increased plaque progression because of elevated levels of leukocyte infiltration and lipid accumulation, while also inducing matrix degradation. Acute and focal mast cell activation in advanced, unstable lesions may induce leakage of pre-existing microvessels leading to intraplaque hemorrhage or may even lead to rupture of the fibrous cap on release of the mast cell–specific proteases. These events could potentially lead to thrombosis and acute cardiovascular events. Depending on the trigger and stage of the plaque, mast cell activation may thus have differential effects on plaque composition and fate. To summarize, mast cells secrete several proatherogenic mediators in the plaque (Table 2), which culminate in increased leukocyte adhesion and influx, matrix degradation, enhanced foam cell formation, vascular cell apoptosis, and microvessel growth, all contributing to plaque progression and destabilization (Figure).

### Table 1. Mast Cells in Atherosclerosis: In Vivo Evidence

<table>
<thead>
<tr>
<th>Author</th>
<th>Findings</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bot et al</td>
<td>Systemic and local mast cell activation in apoE−/− mice leads to plaque progression and destabilization</td>
<td>21</td>
</tr>
<tr>
<td>Sun et al</td>
<td>Atherosclerosis is reduced in LDLr−/− Kit(W−/−/W−/−), and can be restored by repopulation with BMMCs, dependent on IFNγ and IL-6</td>
<td>22</td>
</tr>
<tr>
<td>Heikkilä et al</td>
<td>Atherosclerosis is reduced in LDLr−/− Kit(W−/−/W−/−) because of reduced plasma lipids and reduced inflammation.</td>
<td>23</td>
</tr>
<tr>
<td>Tang et al</td>
<td>Compound 48/80 induced mast cell activation in apoE−/− mice aggravates atherosclerosis</td>
<td>24</td>
</tr>
<tr>
<td>Wang et al</td>
<td>Cromolyn inhibits mast cell–induced atherosclerosis in LDLr−/− mice.</td>
<td>25</td>
</tr>
<tr>
<td>Zhi et al</td>
<td>Overexpression of tryptase enhances the incidence of intraplaque hemorrhage</td>
<td>37</td>
</tr>
<tr>
<td>Uehara et al</td>
<td>Inhibition of chymase inhibits atherosclerosis in hamsters.</td>
<td>47</td>
</tr>
<tr>
<td>Bot et al</td>
<td>Inhibition of chymase inhibits atherosclerosis in apoE−/− mice.</td>
<td>48</td>
</tr>
<tr>
<td>Guo et al</td>
<td>Tranilast reduces atherosclerosis in hamsters.</td>
<td>49</td>
</tr>
<tr>
<td>Kokkonen et al</td>
<td>Mast cell activation enhances lipid uptake by macrophages.</td>
<td>52–55</td>
</tr>
<tr>
<td>Foks et al</td>
<td>Interference in the OX40–OX40L signaling inhibits atherosclerosis partly via reducing mast cell numbers.</td>
<td>64</td>
</tr>
<tr>
<td>den Dekker et al</td>
<td>TLR4-mediated mast cell activation induced plaque VSMC apoptosis.</td>
<td>70</td>
</tr>
<tr>
<td>Bot et al</td>
<td>LPA-induced mast cell activation induces intraplaque hemorrhage.</td>
<td>72</td>
</tr>
<tr>
<td>de Vries et al</td>
<td>Mast cell activation enhances intimal hyperplasia and C5a induces vein graft thickening in a mast cell–dependent manner.</td>
<td>75</td>
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<tr>
<td>Bot et al</td>
<td>Substance P induces mast cell activation and acute plaque destabilization.</td>
<td>77</td>
</tr>
<tr>
<td>Lagrauw et al</td>
<td>Overexpression of Neuropeptide Y enhances plaque development partly by inducing mast cell activation</td>
<td>78</td>
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</tbody>
</table>

IFN indicates interferon; LDLr, low-density lipoprotein receptor; LPA, lysophosphatidic acid; TLR4, toll-like receptor 4; and VSMC, vascular smooth muscle cells.
VEGF can induce plaque progression, macrophage infiltration, and matrix degradation, plaque destabilization, and intraplaque hemorrhage. 

Heparin binds LDL, enhances foam cell formation.

Histamine enhances vessel permeability, induces vascular leakage, increases incidence of intraplaque hemorrhage, and induces macrophage apoptosis.

Tryptase induces CCL2 and IL-8 expression by endothelial cells, matrix degradation, plaque destabilization, and induces macrophage apoptosis.

Chymase induces matrix degradation, plaque destabilization, generates dysfunctional HDL, thereby reducing the capacity to induce cholesterol efflux from macrophage foam cells, and induces apoptosis of endothelial cells, vascular smooth muscle cells, macrophages, and induces neutrophil recruitment increased incidence of intraplaque hemorrhage.

IL-6 upregulates adhesion molecules on endothelial cells and enhances atherosclerotic plaque progression.

IL-8 induces leukocyte recruitment to the atherosclerotic plaque.

IFNγ enhances atherosclerotic plaque progression.

TNFα upregulates adhesion molecules on endothelial cells.

CCL2 induces leukocyte recruitment to the atherosclerotic plaque.

VEGF can induce plaque neovascularization.

bFGF can induce plaque neovascularization.

**Figure.** Potential roles of activated mast cells in growth and destabilization of an atherosclerotic plaque. A subendothelial mast cell is activated to exocytose a fraction of its cytoplasmic secretory granules. The exocytosed granules contain an array of proinflammatory and proatherogenic effector molecules. Depending on the stage of atherosclerosis, 1 effector molecule may have different modes of action both on plaque progression or destabilization, as indicated. During early atherogenesis (left, plaque growth), the effector molecules stimulate leukocyte recruitment and lipid accumulation in the evolving plaque, whereas during advanced stages of atherogenesis (right, plaque destabilization), they contribute to the generation of an unstable plaque susceptible to rupture. bFGF indicates basic fibroblast growth factor; CCL2, CC chemokine ligand 2; HDL, high-density lipoprotein; IFN, interferon; IL, interleukin; LDL, low-density lipoprotein; MMP, matrix metalloproteinase; and TNF, tumor necrosis factor.

**Table 2. Potential Effects of Mast Cell Mediators on the Atherosclerotic Plaque**

<table>
<thead>
<tr>
<th>Mast Cell Mediator</th>
<th>Effects</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heparin</td>
<td>Binds LDL, enhances foam cell formation</td>
<td>52–55</td>
</tr>
<tr>
<td>Histamine</td>
<td>Enhances vessel permeability, induces vascular leakage, increased incidence of intraplaque hemorrhage, and induces macrophage apoptosis</td>
<td>21</td>
</tr>
<tr>
<td>Tryptase</td>
<td>Induces CCL2 and IL-8 expression by endothelial cells, matrix degradation, plaque destabilization, and induces macrophage apoptosis</td>
<td>30–38</td>
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<tr>
<td>Chymase</td>
<td>Matrix degradation, plaque destabilization, generates dysfunctional HDL, thereby reducing the capacity to induce cholesterol efflux from macrophage foam cells, and induces apoptosis of endothelial cells, vascular smooth muscle cells, macrophages, and induces neutrophil recruitment increased incidence of intraplaque hemorrhage</td>
<td>21, 39–51</td>
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<tr>
<td>IL-6</td>
<td>Upregulation of adhesion molecules on endothelial cells and enhances atherosclerotic plaque progression</td>
<td>22, 57</td>
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<tr>
<td>IL-8</td>
<td>Induces leukocyte recruitment to the atherosclerotic plaque</td>
<td>21, 56</td>
</tr>
<tr>
<td>IFNγ</td>
<td>Enhances atherosclerotic plaque progression</td>
<td>22</td>
</tr>
<tr>
<td>TNFα</td>
<td>Upregulation adhesion molecules on endothelial cells</td>
<td>57</td>
</tr>
<tr>
<td>CCL2</td>
<td>Induces leukocyte recruitment to the atherosclerotic plaque</td>
<td>67, 72</td>
</tr>
<tr>
<td>VEGF</td>
<td>Can induce plaque neovascularization</td>
<td>18</td>
</tr>
<tr>
<td>bFGF</td>
<td>Can induce plaque neovascularization</td>
<td>19</td>
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</tbody>
</table>

Basophil and mast cell genes as measured by genomic profiling of whole blood. In experimental atherosclerosis, IgE was shown to promote plaque expansion because mice deficient in the Fce receptor developed smaller atherosclerotic plaques, but no definitive relationship between mast cell activation and atherosclerosis was established in this study. In another study, interference in the OX40-OX40L signaling pathway was seen to induce regression of atherosclerosis, which was at least partly explained by reduced plasma IgE levels and a concomitant reduction in mast cell numbers and activation status. In contrast to above studies in human populations, plasma IgE levels and low-density lipoprotein oxidation failed to correlate in an Asian patient cohort, and furthermore, in line with this observation, plasma total IgE levels did not show any correlation with disease progression or mast cell numbers in a Western population. For that matter, neither lesional mast cell numbers nor disease state associated with plasma IgG or oxidized LDL–IgG levels in that study although oxidized LDL–IgG immune complexes have been shown to activate...
human mast cells via Fcγ receptors in culture.67 Thus, we may surmise that circulating factors that have entered the atherosclerotic plaque or factors that have been formed in the plaque may be stronger determinants of local mast cell activation, and that such effects may not necessarily be reflected by the corresponding systemic parameters. For example, plaque lipids may be directly involved in mast cell activation in the vessel wall. Oxidized LDL has been shown to induce mast cell activation and subsequent leukocyte recruitment68 and to induce secretion of proatherogenic cytokines via toll-like receptor 449. In this regard, toll-like receptor 4–mediated mast cell activation has recently been reported to induce plaque destabilization.70 Also, individual components of modified LDL particles may act as local mast cell activators, such as lysophosphatidic acid, which was demonstrated to accumulate during lesion progression71 and to induce plaque destabilization in a mast cell–dependent manner.72 Blockade of the lysophosphatidic acid receptor 1 (LPA1) may be of therapeutic interest in this context, and analysis of other (lyso)phospholipids could even lead to the discovery of more potent mast cell activators.

Another potential mast cell activation mechanism acts via the complement system. Mast cells within the plaque have been shown to express receptors for specific complement components, in particular, of the receptor for C5a, C5aR.73 Furthermore, activated complement is present within the atherosclerotic plaque,74 thus fueling the hypothesis of complement-mediated mast cell activation. Indeed, local activation of mast cell with C5a led to an increase in vein graft atherosclerosis, which could be inhibited by the mast cell stabilizer cromolyn.75 Finally, mast cell degranulation, particularly in the adventitia, may be regulated via neuronal activation. In human specimens, mast cells have been found to connect with nerve fibers,76 which were, for example, substance P–positive. Mast cells express a variety of receptors for neuropeptides, such as the substance P, which renders neuropeptide–mediated mast cell activation a likely mechanism, in particular, during episodes of acute stress. In fact, local substance P–mediated mast cell activation resulted in plaque destabilization as indicated by increased intraplaque hemorrhage, which did not occur in mast cell–deficient ApoE−/−/Kit(W-sh/W-sh) mice, suggestive of a mast cell–dependent mechanism.77 Furthermore, also neuropeptide Y has been recently shown to induce atherosclerotic lesion progression, at least partly via increased perivascular mast cell activation.78 Together, these data establish that neuropeptides may act as potential mast cell activators in atherosclerosis, and that they directly link neuronal activation to vascular inflammation and possibly to acute cardiovascular events. To summarize, experimental in vitro and in vivo studies have provided us with several potential mast cell activators in atherosclerosis (Table 3); however, one must realize that the actual endogenous triggers for mast cell activation in patients with cardiovascular diseases are still enigmatic and needs to be defined in future work.

Conclusions

Current evidence clearly points toward a key role for mast cells as effector cells in atherosclerosis and ACS (Table 1). The many mechanisms involved in the effector functions involve secretion of the proteases chymase and tryptase, histamine, growth factors, and cyto- and chemokines, such as tumor necrosis factor-α, interferon γ, interleukin-6, and interleukin-8 by activated mast cells (Table 2). Mast cell activation leads to increased plaque progression and destabilization as illustrated by increased lipid uptake, leukocyte influx, apoptosis, matrix degradation, and intraplaque hemorrhage, as summarized in the Figure. Although the specific endogenous mast cell activators are not known yet, in vivo studies have supplied several potential candidates, which all act via different receptors, and thus result in different release patterns and disease outcome (Table 3). General mast cell stabilizers, which have been shown to be effective in halting plaque progression and destabilization in animal models, are already commonly used in the clinic, rendering their use in patients with ACS potentially feasible. However, inhibition of specific pathways of atherosclerosis–induced mast cell activation would be preferable instead of systemic mast cell stabilization because the latter may interfere with beneficial mast cell functions, for example, such involved in host defense responses or wound healing. Importantly, effects of mast cell inhibitors on mast cell–dependent tissue repair need to be thoroughly investigated. Additional research will also be aimed at identifying specific mast cell recruitment pathways to the vessel wall and at elucidating particular communication pathways and cellular interactions of mast cells with other cell types within the plaque. Furthermore, an in-depth analysis of lesional mast cell phenotypes may provide further insight in potential atherosclerosis–specific therapeutic strategies to halt mast cell–dependent plaque destabilization.

In conclusion, because mast cells seem to contribute to atherosclerosis and in particular, plaque destabilization markedly, additional studies identifying specific intervention strategies are urgently needed because they can open novel therapeutic avenues in the prevention of ACS.

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<table>
<thead>
<tr>
<th>Activator</th>
<th>Described Mediators in Releasate</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgE</td>
<td>Degranulation via crosslinking of FcγRs, resulting in release of proteases, growth factors, cytokines etc</td>
<td>58</td>
</tr>
<tr>
<td>oxLDL–IgG immune complexes</td>
<td>Cytokine release, specifically of TNFα, IL-8, and CCL2 via Fcγ receptors</td>
<td>67</td>
</tr>
<tr>
<td>OxLDL</td>
<td>Induces albumin leakage in vivo, possibly via histamine release, and induces the release of TNFα, IL-6, and CCL2 via TLR4 in vitro</td>
<td>68, 69</td>
</tr>
<tr>
<td>LPS</td>
<td>Not only cytokines, such as IL-6, but also some release of proteases via TLR4</td>
<td>70</td>
</tr>
<tr>
<td>LPA</td>
<td>Release of tryptase and CCL2 via LPA1</td>
<td>72</td>
</tr>
<tr>
<td>C5a</td>
<td>Release of tryptase and CCL2 via C5aR</td>
<td>75</td>
</tr>
<tr>
<td>Substance P</td>
<td>Chymase and tryptase via NK R</td>
<td>77</td>
</tr>
<tr>
<td>Neuropeptide Y</td>
<td>Tryptase and IL-6</td>
<td>78</td>
</tr>
</tbody>
</table>

CCL2 indicates CC chemokine ligand 2; IL, interleukin; LPA, lysophosphatidic acid; oxLDL, oxidized low-density lipoprotein; TLR4, toll-like receptor; and TNF, tumor necrosis factor.
Disclosures

None.

References


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