Circulation

IN DEPTH

Role of Allergic Inflammatory Cells in Coronary Artery Disease

ABSTRACT: Inflammation is an important player both for the initiation and progression of coronary artery disease and for coronary plaque instability. Moreover, inflammation contributes to stent thrombosis and in-stent restenosis after percutaneous coronary intervention. In the past several decades, most studies evaluated the involvement of cellular effectors of classic inflammatory responses, such as monocytes/macrophages, neutrophils, and T cells. Yet, besides classic inflammation, mounting evidence derived from both experimental and clinical studies suggests an important, often unrecognized, role for effector cells of allergic inflammation in both the pathogenesis of coronary artery disease and adverse events following stent implantation. In this review, we discuss the role of effector cells of allergic inflammation in the setting of coronary artery disease progression and instability, and in the occurrence of adverse events following stent implantation, as well. Moreover, we discuss possible therapeutic approaches targeting different specific pathways of allergic inflammatory activation.

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Inflammation is a key feature of atherosclerosis and represents a well-known pathogenic mechanism underlying both coronary plaque progression and instability and adverse events following stent implantation.[1–3] In particular, classic inflammatory responses mainly mediated by macrophages, Th1 lymphocytes, and neutrophils have been shown to play an important role.[1,2] This notion has recently been validated in the landmark CANTOS trial (Canakinumab Anti-Inflammatory Thrombosis Outcomes Study)[4] showing that pharmacological interleukin-1β (IL-1β) inhibition was associated with a significant lower rate of recurrent cardiovascular events in comparison with placebo, irrespective of lipid-lowering therapy in patients with a previous history of myocardial infarction. In particular, the reduction of high-sensitivity C-reactive protein levels to <2 mg/L was associated with a reduction of the relative risk of cardiovascular and all-cause mortality by 31%.[5] Therefore, there is now clear-cut evidence that blunting the classical inflammatory cascade mitigates the risk of adverse events linked to coronary artery disease (CAD).[6]

However, besides classic inflammatory reactions, there is also evidence suggesting that effector cells of allergic inflammation may play a role in coronary artery plaque progression and instability, and in adverse reactions following coronary stent implantation, as well.[7–10] Initially described by Paul Ehrlich,[10a] mast cells and eosinophils play a pivotal role in allergic inflammation. The evidence of reciprocal modulation of functions between these 2 cells through soluble mediators leads

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to the definition of "allergic effector unit."[11] Moreover, besides the well-known systemic IgE-dependent pathway of allergic inflammatory activation, these cells are also endowed with a large repertoire of receptors allowing them to respond to different IgE-independent local or systemic stimuli. Once activated, mast cells and eosinophils release a plethora of cytokines, growth factors, and vasoactive agents able to mediate tissue inflammation and remodeling.[11]

In this review, we discuss the role of effector cells of allergic inflammation in the context of CAD progression and instability, and in the occurrence of adverse events following stent implantation, as well. Moreover, we suggest possible therapeutic approaches targeting different specific pathways of allergic inflammatory activation.

ALLERGIC INFLAMMATION AND CORONARY PLAQUE PROGRESSION

Leukocyte recruitment and expression of proinflammatory cytokines within the arterial wall characterize all steps of atherothrombosis.[1,2] Different subsets of leukocytes mediating classic inflammatory responses, such as monocytes/macrophages, neutrophils, and T cells, have been shown to be involved in the process of atherogenesis.[1,2] However, many studies demonstrated that cellular mediators of allergic inflammation also may play a role in coronary artery plaque formation and progression (Figure 1).

Prospective studies showed an association between eosinophil count and increased risk for future cardiovascular events.[12] Furthermore, eotaxin, an eosinophil-specific chemoattractant, is overexpressed by smooth muscle cells on tumor necrosis factor-α stimulation in human atherosclerotic lesions,[13] and patients with CAD have higher circulating levels of eotaxin than healthy controls.[14] Accordingly, a polymorphism in the eotaxin gene[15] affecting eosinophil count and associated with a higher risk of allergic inflammatory reaction[16] has recently been associated with an increased risk of myocardial infarction. However, pathological studies demonstrated that eosinophils are rarely observed in human atherosclerotic lesions,[13] suggesting that overexpression of eotaxin and its receptor, CCR3, in the inflammatory infiltrate of human atheroma has functions other than eosinophil recruitment and activation. Indeed, because CCR3 receptor is predominantly expressed by macrophages, it is possible that eotaxin modulates macrophage function. Moreover, because CCR3 receptor was also identified on mast cells, eotaxin may be involved in mast cell activation and recruitment.[15] However, several lines of evidence might suggest a role for eosinophil-derived mediators in coronary atherosclerosis progression. In particular, eosinophil cationic protein (ECP) is a zinc-containing, highly cationic protein, stored in the peroxidase-positive and -negative eosinophil granules, which is secreted by eosinophils through priming by various triggers, such as immunoglobulins and complement components.[17] ECP is involved in multiple biological activities. Indeed, in addition to its cytotoxic activity,[18] ECP upregulates intercellular adhesion molecule 1 expression on endothelial cells,[19] allowing monocyte adhesion on endothelium and, in turn, favoring atherogenesis. Moreover, ECP modulates fibroblast activity, leading to increased proteoglycan deposits and extracellular matrix formation,[20] which might have a stabilizing effect on plaque growth. ECP represents a marker of eosinophil activity, and increased serum ECP levels are related to the presence and severity of asthma and other allergic diseases.[21] A study by our group[8] recently demonstrated that patients with higher serum ECP levels have an increased coronary atherosclerotic burden and the use of ECP, added to main cardiovascular risk factors, improves the classification performance for the diagnosis of angiographically detectable coronary atherosclerosis among patients undergoing coronary angiography because of chest pain. Of importance, the addition of C-reactive protein further improves the classification performance, suggesting that ECP and C-reactive protein may reflect different aspects of CAD. Indeed, ECP is associated with the burden of coronary atherosclerosis, whereas C-reactive protein is associated with the presence of a more complex plaque morphology.[8] Finally, activated eosinophils release interferon-α and interferon-β modulating macrophage function[22] and favoring foam cell formation.[23]

Besides a possible role for eosinophils and their mediators, conflicting data are available regarding the role of interleukin-5 (IL-5) in atherosclerosis. IL-5 belongs to a group of cytokines collectively called eosinopoietins (including also IL-3 and granulocyte-macrophage colony-stimulating factor) and plays a pivotal role in maturation, differentiation, activation, and survival of eosinophils.[24] Previous experimental studies demonstrated that Th2-mediated responses had atheroprotective effects in mice, mainly mediated by IL-5 and IL-13 release.[25] However, clinical studies failed to demonstrate a convincing atheroprotective role in humans for IL-5.[26,27] On the contrary, patients with unstable angina had higher serum levels of IL-5,[28] and staining for IL-5 was identified in inflammatory cells within coronary thrombi.[29] At the same time, the atheroprotective role of IL-13 and of Th2-mediated responses is also debated. Indeed, specific haplotypes of the *IL-13* gene are associated with a higher risk of developing CAD in the Chinese population[30]; and during allergic inflammatory response, Th2 cells can release IL-9, a cytokine able to promote atherosclerotic plaque formation in ApoE$^{-/-}$ mice.[31] Moreover, IL-9 levels were also

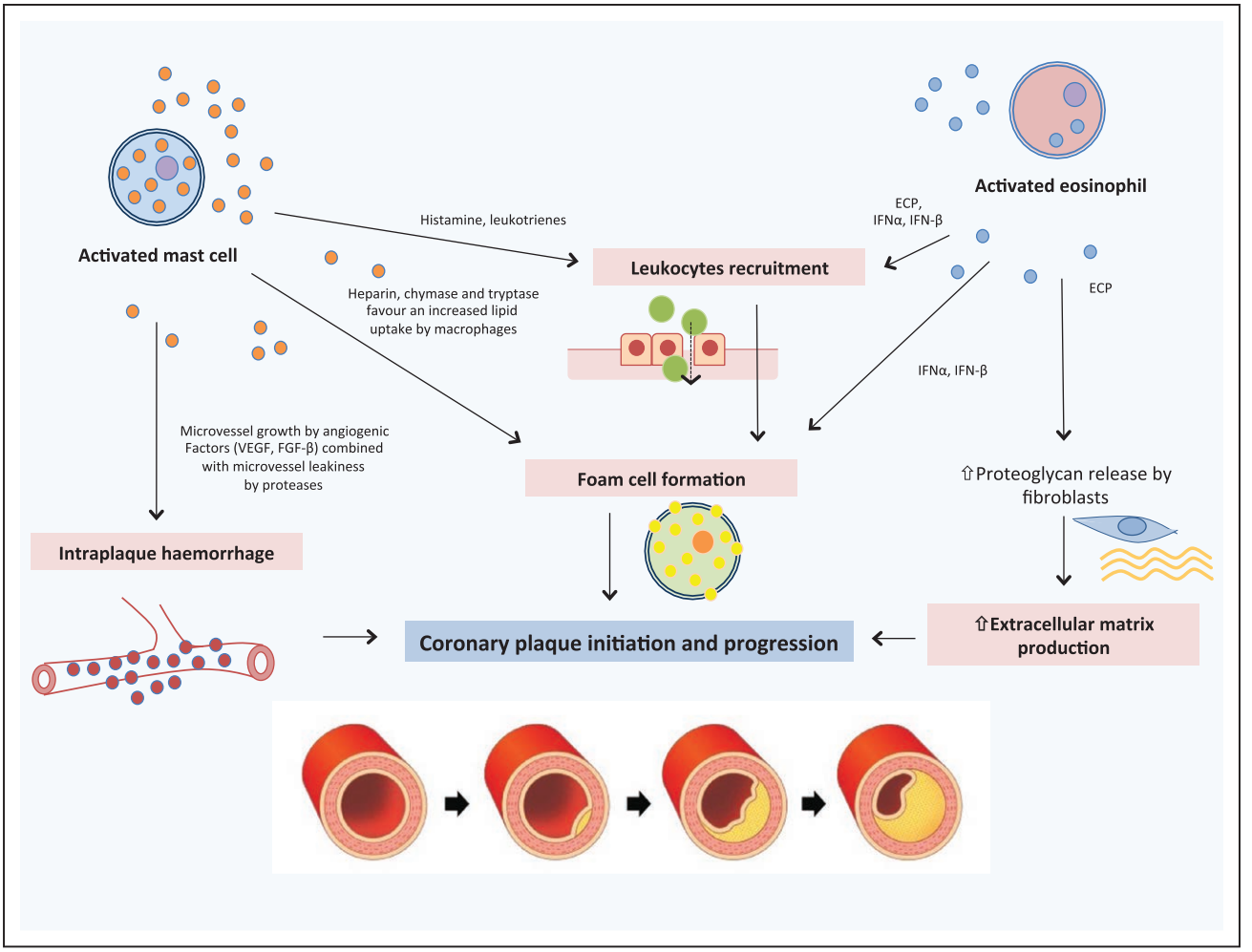

Figure 1. The role of allergic inflammatory cells in coronary atherosclerosis initiation and progression.
ECP indicates eosinophil cationic protein; FGF-β, fibroblast growth factor-β; IFN, interferon; and VEGF, vascular endothelial growth factor.

increased in plasma and carotid plaques of patients with carotid and coronary atherosclerosis.[32]

Mast cells are another important mediator of allergic inflammatory reactions. All mast cells contain the protease tryptase, and a fraction of them also contains chymase and other granule proteases. In the early stage of atherogenesis, mast cells migrate and accumulate in the arterial intima and in the adventitia[33–35] as a consequence of the interaction between chemokine eotaxin and the receptor CCR3 expressed on the mast cell.[36] It is interesting that apoE-deficient mice treated with a CCR3 signaling antagonist showed reduced mast cell recruitment in the atherosclerotic lesion and reduced plaque progression.[37] At later stages of atherogenesis, mast cell progenitors may migrate from the adventitia into the plaque through neovessels that originate from vasa vasorum.[38] Of importance, mast cells tend to locate near plaque microvessels, and, by releasing angiogenic molecules (ie, vascular endothelial growth factor and basic fibroblast growth factor), they induce microvessel growth.[39] At the same time, mast cells may be involved in coronary plaque growth causing intraplaque hemorrhage as a consequence of microvessel leakiness and disruption by release of matrix-degrading proteases.[40] Accordingly, in the mast cell–deficient LDLr$^{-/-}$ Kit(W^{-sh}/W^{-sh}) mouse, lack of mast cells was associated with a decrease in lesion size.[41] It is interesting to note that, in a human autopsy study, plaque tryptase and chymase levels were shown to increase proportionally with lesion size[42]; and, in a study in the murine model, overexpression of tryptase caused more intraplaque hemorrhage, which was inhibited by a tryptase targeting small interfering RNA.[43] Moreover, activated mast cells release histamine and leukotrienes, potent vasoactive inflammatory molecules, that increase vascular permeability and activate endothelial cells and, in turn, favor the entry of circulating low-density lipoprotein (LDL) and inflammatory cells in the arterial intima.[44] Finally, mast cell activation may contribute to atherosclerosis progression, also enhancing lipid uptake by macrophages and inducing the formation of foam cells.[38,45]

Mechanisms of activation of eosinophils and mast cells are multiple (Table 1). Eosinophils may be activated by cytokines (ie, IL-5, tumor necrosis factor-α),

Table 1. Factors Potentially Involved in Recruitment and Activation of Allergic Inflammatory Cells in the Setting of Coronary Atherosclerosis

Factor	Mechanism	References
Mast cells		
IgE	Environmental exposure to an allergen that interacts with FcεR1 present on mast cell membrane	38
CCR3	Involved in eotaxin-mediated recruitment in the atherosclerotic plaque	13
oxLDL	Interaction with TLR-4	38,48
oxLDL-IgG complexes	Local or circulating immune complexes oxLDL-IgG that interact with FcγR present on mast cell membrane	50
Complement system protein (ie, C5a and C3a)	Interaction with specific complement receptors (C5aR or C3aR)	49
LPS	Interaction with TLR-4	38,48
LPA	Possible interaction with TLR-4	38
Neuropeptides (substance P, neuropeptide Y)	Interaction with neurokinin-1 receptor, MRGPRX2	70–72
Eosinophils		
IL-5	Cytokine released by Th2 cells and mast cells that induces eosinophil maturation and activation	24,46
TNF-α	Proinflammatory cytokine involved in eosinophil recruitment and activation	46
Histamine	Interaction with H1 and, most importantly, H4 receptors on eosinophil membrane with subsequent eosinophil recruitment and intracellular calcium mobilization	38
PAF	Interaction with both PAFR-dependent and independent pathways and subsequent release of cationic proteins	46
oxLDL	Eosinophil activation and degranulation, in part mediated by CD36 scavenger receptor	22

CCR3 indicates CC chemokine receptor 3; Ig-E, immunoglobulin E; IgG, immunoglobulin G; IL-5,: interleukin-5; LPA, lysophosphatidic acid; LPS, lipopolysaccharide; MRGPRX2, Mas-related G-protein–coupled receptor-X2; oxLDL, oxidized low-density lipoprotein; PAF, platelet-activating factor; PAFR, platelet-activating factor receptor; TLR-4, toll-like receptor 4; and TNF-α, tumor necrosis factor-α.

histamine, and platelet-activating factor.[46] Moreover, experimental studies demonstrated that oxidized LDL might also be involved in eosinophil activation, in part, mediated by CD36 scavenger receptor.[22] Regarding mechanisms of activation of mast cells, the IgE-dependent pathway via allergen-triggered cross-linking of IgE molecules bound to Fcε receptors on the mast cell surface is the best known because of its role in allergy. It is interesting to note that IgE levels have been shown to be higher in patients with unstable angina pectoris than in control subjects.[47] Moreover, IgE can promote the formation of complexes of Fcε receptors and Toll-like receptor 4, suggesting possible mast cell activation by Toll-like receptor 4 agonist lipopolysaccharide and by oxidized LDL present in the plaque.[38,48] It is important to note that IgE-independent pathways may also activate mast cells. Indeed, mast cells express receptors for specific complement components (ie, C5a, C5aR)[49] that are present within the atherosclerotic plaque. Moreover, mast cells also express Fcγ receptors that mediate mast cell activation by complexes of IgG and oxidized LDL.[50] It is noteworthy that mast cells may also contribute to recruitment and activation of eosinophils by the release of histamine and platelet-activating factor.[38] Finally, epidemiological studies have shown a positive association between obesity, serum tryptase levels, and the risk of asthma, and obese or diabetic patients present a higher number of activated mast cells in the adipose tissue in comparison with normal weight or nondiabetic patients.[38] These data represent a link between mast cells, metabolic disorders, and the risk of developing CAD.

ALLERGIC INFLAMMATION AND CORONARY PLAQUE INSTABILITY

Mechanisms underlying coronary plaque instability are multiple.[3] Plaque rupture with systemic signs of inflammatory activation and local inflammatory cell infiltration is the most frequent mechanism causing acute coronary syndrome (ACS).[3,51] Among inflammatory cells, classic inflammatory cells, such as macrophages, lymphocytes, and neutrophils, have been extensively studied in the pathogenesis of coronary instability.[3] However, some recent studies have suggested that, at least in a subset of patients, cellular mediators of allergic inflammatory responses, in particular, eosinophils, basophils, and mast cells, may also play a pathogenetic role[10] (Figure 2).

Several studies demonstrated that eosinophils may favor thrombus formation and enhance coronary vasoconstriction[32,52,53] (Table 2). Indeed, eosinophil granule proteins, in particular, ECP, have been shown to activate platelets and promote thrombus formation by inhibiting the function of thrombomodulin.[54] In addition, activated eosinophils release potent peroxidase products that can induce a proinflammatory and prothrombotic state in endothelial cells.[55] Accordingly, numerous reports of thrombotic events in patients with eosinophil-related disorders, such as hypereosinophilic syndrome, suggested an involvement of eosinophils in this process. It was estimated that one-quarter to nearly one-half of patients affected by hypereosinophilic syndrome develop thromboembolic complications. In particular, venous thrombosis (ie, portal veins, cerebral) and intra-

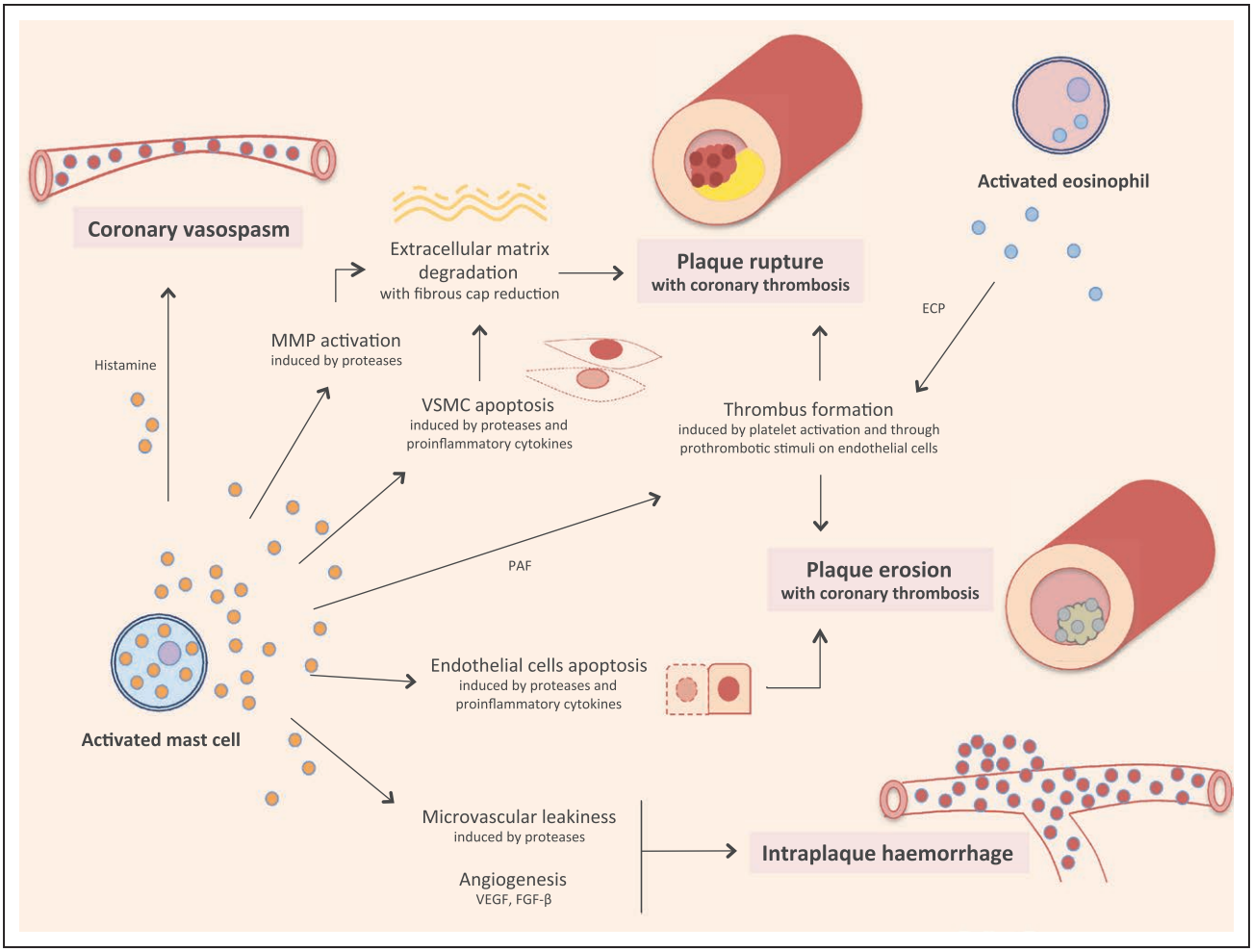

Figure 2. The role of allergic inflammatory cells in coronary plaque instability.
ECP indicates eosinophil cationic protein; FGF-β, fibroblast growth factor-β; MMP, matrix metalloproteinases; PAF, platelet activated factor; VEGF, vascular endothelial growth factor; and VSMC, vascular smooth muscle cells.

cardiac thrombosis involving the left or right ventricle or both are the most common presentations. Most arterial occlusions are secondary to peripheral embolism from intracardiac thrombi or vasculitis, and occlusive coronary thrombosis has also been reported.[56] Recently, we demonstrated that degranulation of eosinophil cells and activation of basophil cells may be involved in the pathogenesis of ACS.[10] In particular, using flow cytometry analysis, we found a greater expression of CD69 and CD203c, markers of eosinophil degranulation and of basophil activation, respectively, in patients with ACS in comparison with patients with stable angina. CD69 expression on eosinophils is induced by some eosinophil-active cytokines (granulocyte-macrophage colony-stimulating factor, IL-3, and IL-5) and might trigger platelet aggregation and degranulation via phospholipase A2 activation and subsequent release of thromboxane A2.[57,58] This linking with platelet activation supports the notion that CD69 might have a role in plaque destabilization and thrombus formation during ACS. Accordingly, histopathologic studies in patients with ACS reported a greater eosinophil infiltration in larger red thrombi, but not in the underlying atherosclerotic plaques,[29] suggesting a role for systemic activation of eosinophils, rather than local, in coronary plaque instability. In the same study,[10] we measured systemic ECP levels in a population of patients with ST-segment–elevation myocardial infarction at the time of primary percutaneous coronary intervention, demonstrating that serum levels of ECP predicted major adverse cardiac events at 24 months, independently of the baseline ejection fraction. This predictive role might be explained, at least in part, by the higher thrombus score associated with raised ECP levels. Moreover, eosinophils and basophils are source of IL-17, a cytokine that has recently been suggested to be involved with controversial data in coronary instability.[59] Basophil cells, another important player in allergic inflammatory responses, have been assessed in our study[10] by using CD203c, a lineage-specific marker, rapidly upregulated on activation. Its upregulation during ACS highlights that basophil activation may probably contribute to

Table 2. Pathophysiological Effects of Mediators Released by Allergic Inflammatory Cells in the Setting of Coronary Atherosclerosis

Mediator	Biological effects	References
Mast cells		
Tryptase	Activation of MMP with matrix degradation; macrophage apoptosis; microvascular leakiness.	42,43
Chymase	Activation of MMP with matrix degradation; macrophage, endothelial cells and VSMC apoptosis; microvascular leakiness: generation of dysfunctional HDL with reduced cholesterol efflux from macrophages	35,38,42
Histamine	Vasodilation and increased vessel permeability; macrophage apoptosis; eosinophil recruitment	38,44
Heparin	Binds LDL favoring foam cell formation	38,45
VEGF	Increased intraplaque microvascular growth	39
FGF-β	Increased intraplaque microvascular growth	39
CCL2	Leukocyte recruitment into the atherosclerotic plaque	35,38
IL-6, IL-8	Leukocyte recruitment into the atherosclerotic plaque	35,38
PAF	Platelet aggregation, eosinophil activation	38,46,74
Eosinophils		
ECP	Upregulates ICAM-1 expression; stimulates collagen production by fibroblasts; promotes thrombus formation by inhibiting the function of thrombomodulin	17–21
TNF-α	Proinflammatory cytokine	22
VEGF	Increased intraplaque microvascular growth	46
IFN-α, IFN-β	Monocyte/macrophage recruitment in the atherosclerotic plaque, activation and foam cell formation	22
IL-3	Basophil activation mediated by CD203c upregulation	60
Peroxidases	Induction of a proinflammatory and prothrombotic state in endothelial cells	21,55

CCL2 indicates CC chemokine ligand-2; ECP, eosinophil cationic protein; FGF-β, fibroblast growth factor-β; HDL, high-density lipoprotein; ICAM-1, intracellular adhesion molecules-1; IFN, interferon; IL, interleukin; MMP, matrix metalloproteinases; PAF, platelet-activating factor; TNF-α: tumor necrosis factor-α; VEGF, vascular endothelial growth factor; and VSMC, vascular smooth muscle cell.

ACS. The mechanisms remain unknown, but presumably are IgE-independent.[60]

Mast cells may be involved in coronary instability with different mechanisms (Table 2). As described previously, mast cells may favor coronary plaque progression causing intraplaque hemorrhage, which is, at the same time, a well-known mechanism underlying plaque instability. Accordingly, a histopathologic study with specimens of patients undergoing carotid endarterectomy showed that the number of mast cells directly correlated with the incidence of intraplaque hemorrhage, and were also associated with the incidence of future cardiovascular events.[61] In addition, plasma tryptase levels were significantly higher in patients who had a subsequent cardiovascular event after carotid endarterectomy.[61] Moreover, serum tryptase levels measured during index admission in patients with ACS correlated with major adverse cardiovascular events at 2 years[62] and with a more complex CAD (as defined by the SYNTAX score [Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery]) at coronary angiography.[63] However, because other studies failed to show any increase in systemic tryptase levels during cardiovascular events,[64] tryptase effects may be more evident locally within the culprit lesion without any measurable release of tryptase into the systemic circulation. Moreover, tryptase and chymase are able to activate matrix-degrading metalloproteinases possibly leading to the rupture of the plaque fibrous cap.[65] In addition, in advanced atherosclerotic lesions in mice, mast cell activation has been demonstrated to induce the apoptosis of vascular smooth muscle cells and endothelial cells.[66,67] In particular, smooth muscle cell apoptosis causes a reduced matrix production and, together with protease-induced metalloproteinase activation, may induce a reduction in cap thickness and finally plaque rupture. In addition, endothelial cells apoptosis may cause plaque erosion, another important mechanism underlying coronary plaque instability. It is important to note that human pathological studies demonstrated that activated mast cells are present at the sites of plaque rupture or plaque erosion (200-fold more than in the unaffected coronary intima),[33,68] and a higher number of tumor necrosis factor-α–positive mast cells was detected in coronary unstable plaques in comparison with stable plaques.[69]

It is interesting that, along with previously described pathways, activation and degranulation of mast cells located in the arterial adventitia may also be triggered via neuronal activation. Indeed, mast cells have been shown to interact with nerve fibers and neuropeptides (ie, substance P, neuropeptide Y).[70,71] It is noteworthy that, in the murine model, substance P and neuropeptide Y have recently been shown to induce atherosclerotic lesion progression and destabilization, at least in part, via increased perivascular mast cell activation.[72,73] These data suggest that mast cell activation by neuropeptides may be involved in coronary plaque instability, in particular, in episodes of acute stress. Moreover, platelet surface membrane also contains receptors for histamine and platelet-activating factor that are also released from mast cells and may promote platelet aggregation.[74] It is noteworthy that a class of platelets with high- and low-affinity receptors for IgG and IgE on their surface[75] is involved in the activation cascade and is activated during allergic responses.

Coronary vasospasm represents another important mechanism involved in the pathogenesis of ACS.[3] It is important to note that histamine released by activated mast cells may induce coronary vasoconstriction and cause myocardial infarction.[76] In 1991, Kounis and Zavras[77] described the first case of allergic angina syndrome as consequence of a histamine-induced coronary spasm causing an allergic acute myocardial infarction. Kounis syndrome is currently defined as the occurrence of ACS associated with mast cell and platelet activation in the setting of an anaphylactic reaction.[78] The most common triggers of Kounis syndrome are antibiotics (27.4%) followed by insect bites (23.4%).[79] Mast cell degranulation and release of the inflammatory mediators triggered by antigen-antibody reaction on the surface of the mast cells and basophils is the most important underlying pathogenic mechanism.[77–79] This explains the finding that 80% of the cases occur within the first hour of exposure to the trigger. Three types of Kounis syndrome have been described. In type I (most common variant, 72.6%), ACS is a consequence of coronary artery spasm attributable to the release of inflammatory mediators. In type II (22.3%), the release of inflammatory mediators induces coronary artery spasm together with coronary plaque erosion or rupture. Type III (5.1%) includes patients with coronary artery stent thrombosis (ST) as a result of eosinophil and mast cell infiltration.[78]

Finally, systemic mastocytosis, a well-recognized risk factor for anaphylaxis, is a disease characterized by the clonal expansion of mast cells.[80] It is important that the clinical picture of anaphylaxis in those patients is dominated by cardiovascular manifestations including acute coronary events, and systemic mastocytosis by itself represents an independent risk factor for the occurrence of cardiovascular events.[80] Altogether, these data reinforce the concept that mast cells provide a direct contribution to cardiovascular events.

ROLE OF ALLERGIC INFLAMMATION IN ADVERSE EVENTS AFTER STENT IMPLANTATION

Along with technical and mechanical factors, the individual inflammatory response to stent implantation is an important player in in-stent restenosis (ISR) and ST.[81,82] Indeed, experimental studies demonstrated that local and systemic inflammation may promote neointimal proliferation, the leading mechanism involved in the pathogenesis of ISR.[83] Moreover, several evidences suggest a role for inflammation also in the pathogenesis of ST.[84–86] The metal stent struts and the polymer may promote local recruitment and activation of effector cells of allergic inflammation. In particular, IgE-independent phenomena such as type IV hypersensitivity or foreign body–induced activation might be involved, resulting in a delayed arterial healing with incomplete stent reendothelialization and stent malapposition, conditions that may predispose to stent thrombosis[82,84] (Figure 3). Accordingly, eosinophil infiltrates surrounding stent struts have been described in ISR tissue of patients treated with bare metal stents but rarely in postballoon restenotic tissue.[87] It is also worth noting that histopathologic studies showed that eosinophil infiltrates are observed more frequently with drug-eluting stents (DES) than with bare metal stents, suggesting that allergy-mediated inflammation plays a greater role with DES-related ISR than with bare metal stent–related ISR.[88] Pathological evidence supports the notion that hypersensitivity to the polymer is the most relevant mechanism, because polymers have been shown to produce hypersensitivity reactions in humans and to promote inflammation when implanted in swine coronary arteries.[89] Accordingly, we have shown that preprocedural serum ECP levels predict the clinical outcome after implantation of first-generation DES[9] or bare metal stent.[90] In particular, because the target lesion revascularization rate was highly prevalent in the composite end point in comparison with death or myocardial infarction, our findings should mainly be applied to target lesion revascularization. Along with ISR, eosinophils might play a role also in ST. Indeed, eosinophilic infiltrates may induce a coronary arteritis with tissue necrosis and erosion around the stent strut causing vessel remodeling with aneurysmal dilatation and secondary stent malapposition and local thrombosis.[84] In addition, as described above, eosinophils can directly stimulate the coagulation pathway and promote platelet activation.[54–58] Virmani et al[84] first documented a localized hypersensitivity reaction associated with late ST in a patient implanted with a sirolimus-eluting stent. Later, Joner et al[91] reported postmortem findings from a series of 40 patients who died after first-generation DES implantation, showing that the presence of a localized hypersensitivity reaction was a risk factor for the occurrence of late ST. Additional data confirming the association among local hypersensitivity reaction, thrombosis, and lack of intimal healing after DES deployment were shown by the RADAR project (Research on Adverse Drug Events and Reports).[86] Moreover, the RADAR project study evaluated the clinical importance of hypersensitivity reactions to DES, according to the World Health Organization criteria for potential causal agents. Hypersensitivity reactions were defined as the probable cause of symptoms if all other potential causes were scored as unlikely (all medications discontinued) and there was evidence of a persistent allergic response for at least 2 weeks' duration, whereas hypersensitivity reactions were defined as a certain cause

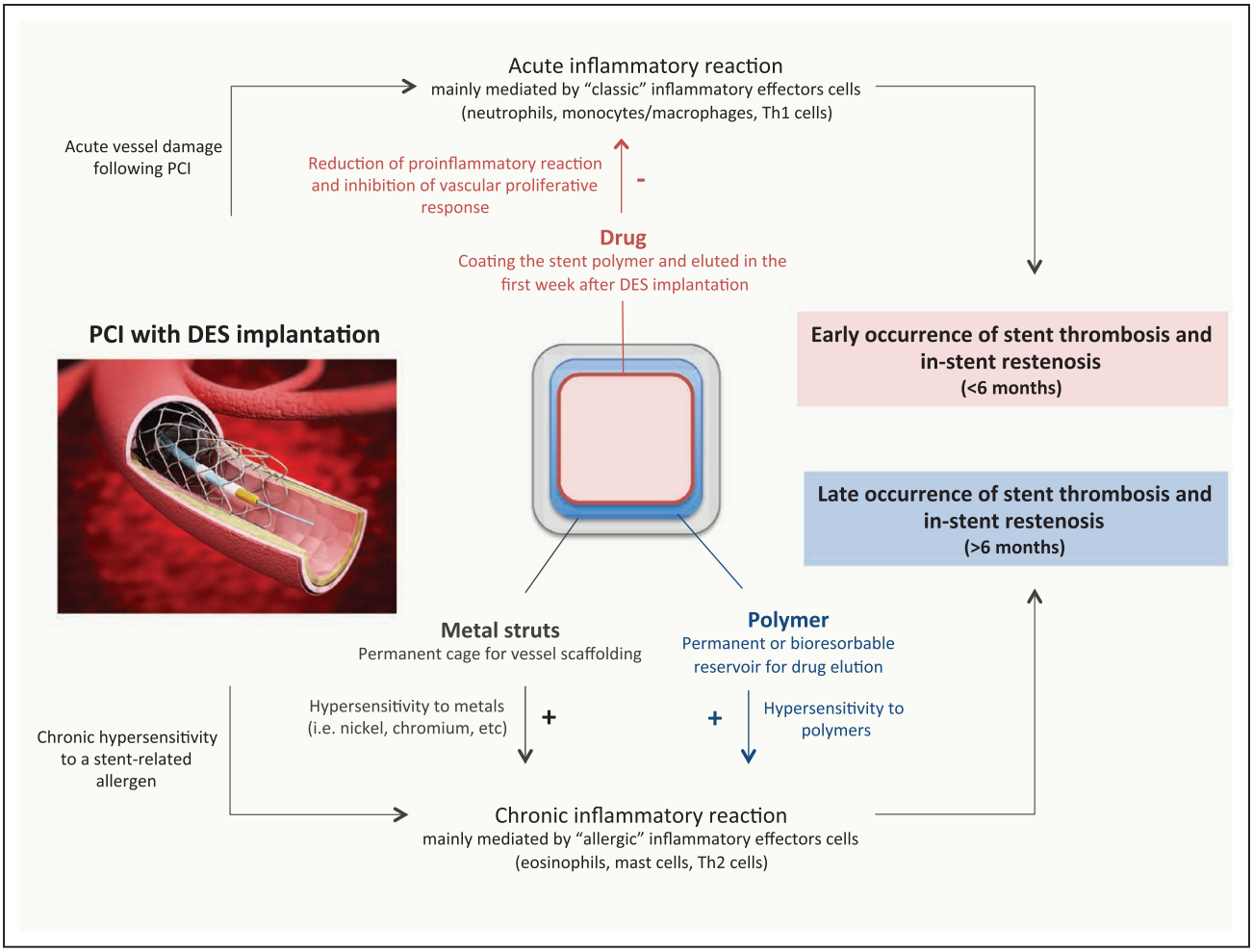

Figure 3. The role of allergic inflammation in adverse reactions after stent implantation.
DES indicates drug-eluting stent; and PCI, percutaneous coronary intervention.

if there was histological evidence of eosinophilic reaction confined to the area of the stent at autopsy. Of note, this study showed that among 17 cases of probable or certain DES-induced hypersensitivity syndromes, 4 patients died of coronary ST, with histological examination demonstrating intrastent eosinophilic infiltrates and poor intimal healing. Moreover, for all 17 cases, DES-induced hypersensitivity reactions were associated with systemic clinical manifestations including nonurticarial rash (n=8), hives (n=5), dyspnea (n=6), myalgia/arthralgia (n=3), itching (n=2), and blisters (n=1). It is noteworthy that 6 of 17 patients required hospitalization because of the severity of symptoms, suggesting that, in an important percentage of patients, the occurrence of a DES-induced hypersensitivity reaction may have significant clinical consequences.[86]

Finally, an initial study of Cook et al[85] showed that eosinophilic infiltrates were more common in thrombi harvested from very late DES thrombosis than in those harvested from other causes of myocardial infarction. In contrast, a more recent study by Riegger et al[92] showed that thrombi harvested from patients with spontaneous myocardial infarction had similar numbers of eosinophils in comparison with ST. However, among different types of DES, significantly more eosinophils were found in aspirates from sirolimus- and everolimus-eluting stents than in paclitaxel- and zotarolimus-eluting stents.[92]

THERAPEUTIC IMPLICATIONS

Although recent studies suggest that treatments targeting classical inflammation have beneficial effects on cardiovascular outcome, specific therapies targeting allergic reactions need to be investigated in the future (Figure 4).

Several studies demonstrated that statins, besides their effects on classical inflammation, may affect mast cell, basophil, and eosinophil responses.[93–95] In particular, fluvastatin has been shown to suppress IgE-mediated basophil and mast cell activation and degranulation targeting the pathway involved in CD203c upregulation.[93,94] Similar effects have been shown for simvastatin.[95]

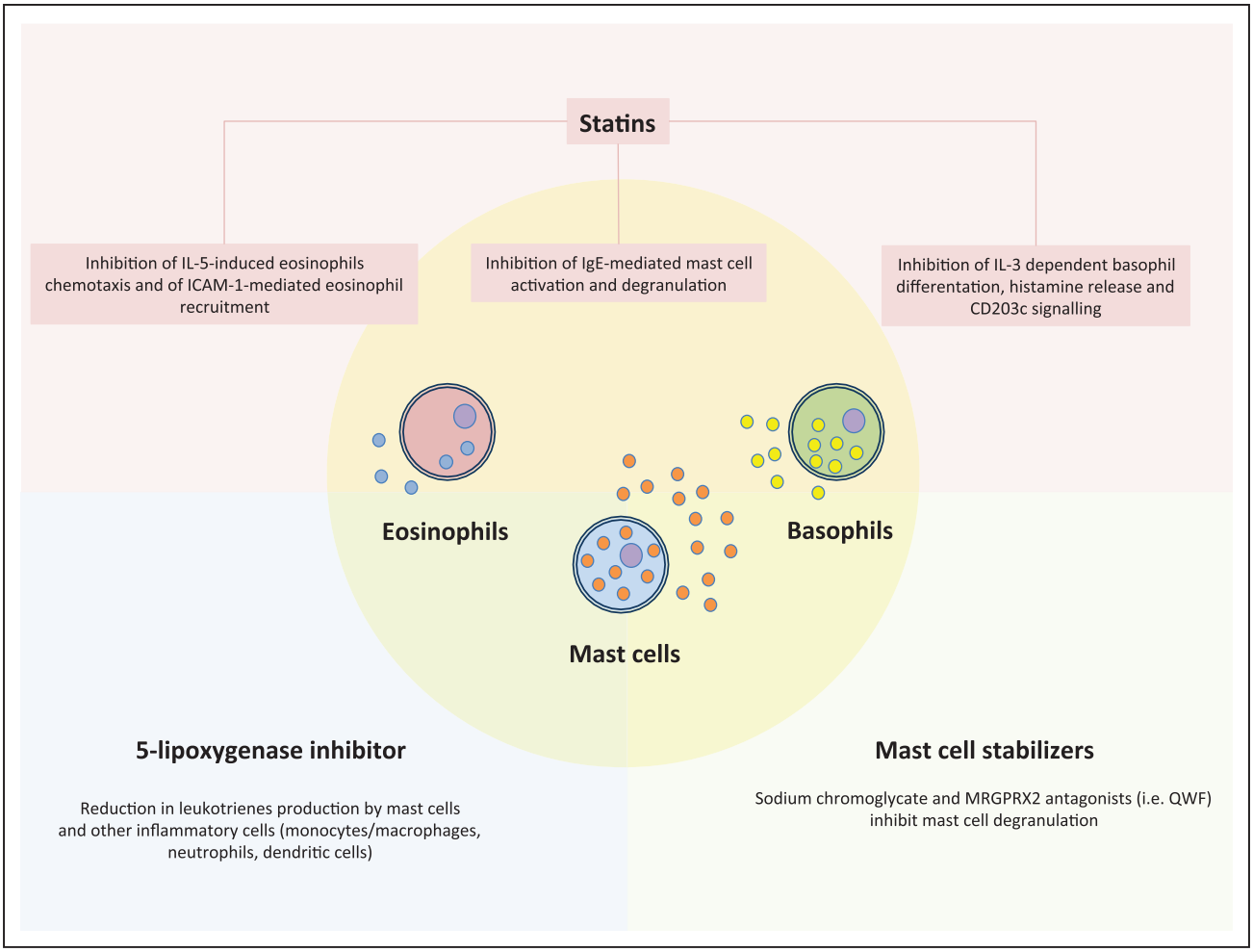

Figure 4. Possible therapeutic approaches targeting allergic inflammatory cells.
ICAM-1 indicates intercellular adhesion molecule 1; IL, interleukin; MRGPRX2, Mas-related G-protein–coupled receptor-2; and QWF, Gln-D-Trp(Formyl)-Phe benzyl ester.

Antileukotriene drugs (leukotriene receptor antagonists or 5-lipoxygenase inhibitors) may represent another possible therapeutic approach to further reduce the allergic response because leukotrienes are involved in a variety of allergic conditions.[96] Leukotrienes represent a class of eicosanoids that are derived through the action of 5-lipoxygenase, an enzyme selectively expressed in bone marrow–derived cells (ie, neutrophils, monocytes, macrophages, dendritic cells, and mast cells) that catalyzes the transformation of arachidonic acid into leukotrienes. These molecules are potent chemoattractants for inflammatory cells and may also increase vascular permeability and contract smooth muscle cells, causing bronchoconstriction and vasoconstriction.[96] It is interesting to note that patients with recent ACS treated with 5-lipoxygenase inhibitor had a reduction in leukotriene production, resulting in a slowed coronary plaque progression at follow-up in comparison with placebo.[97,98]

Moreover, mast cell stabilization with sodium cromoglycate, a drug with >40 years of history in the clinic application for allergic disorders, attenuates experimental atherosclerosis in LDL receptor–deficient (*Ldlr*$^{-/-}$) mice.[99]

Finally, studies have demonstrated that substance P–induced mast cell degranulation and inflammatory properties are mediated via a member of the Mas-related G-protein–coupled receptors (MRGPRs), MRGPRX2. Of importance, this receptor has been suggested as one of the links between cardiovascular events and allergies,[100] and novel mast cell stabilizers, functioning as MRGPRX2 antagonists, such as the compound Gln-D-Trp(Formyl)-Phe benzyl ester known as QWF, might represent novel drugs to reduce the burden of coronary atherosclerosis and its complications.[100]

In conclusion, the convincing evidence of a relevant role played by eosinophils, mast cells, and basophils in coronary artery diseases deserves further investigations. In particular, understanding the specific pathways involved in recruitment and activation of the effector cells of allergic inflammation in the context of coronary disease might reveal novel important therapeutic targets.

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Disclosures

None.

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