Monocytes in Acute Coronary Syndromes

Eduard Shantsila, Gregory Y.H. Lip

Abstract—The aim of this overview is to summarize the available data on the involvement of monocytes in the pathological processes related to the development of acute coronary syndromes and the recovery of damaged areas, the prevention of excessive inflammatory and procoagulant response, and the restoration of microcirculation (angiogenesis). (Arterioscler Thromb Vasc Biol. 2009;29:1433-1438.)

Key Words: monocyte ■ acute coronary syndromes ■ myocardial infarction

Macrophage infiltration is the initial step toward atherosclerotic plaque formation. Consequent apoptosis or death of macrophages is largely responsible for necrotic core generation in the plaque, and the progressive accumulation of free cholesterol results in expansion of the necrotic core. This is perhaps a simplification, because plaque destabilization is a complex process and includes an unbalanced generation of inflammatory cytokines, as well as angiogenic and growth factors promoting pathological plaque neovascularization and matrix metalloproteinases (MMPs) digesting various proteins of extracellular matrix and ultimately resulting in the rupture of the fibrous cap of the plaque leading to intracoronary thrombus formation. Although the mechanisms of plaque destabilization can be mainly attributed to the processes taken places inside the plaque, circulating peripheral blood monocytes are able to generate and secrete mediators of all the major factors involved in plaque destabilization, including inflammation, matrix degradation, and thrombogenesis (supplemental Table I, available online at http://atvb.ahajournals.org). Also, certain monocyte subpopulations possess potent in vitro angiogenic properties and constitute the main part of so-called endothelial progenitor cells (EPCs).

The apparent “success” of myocardial infarction (MI) treatment after restoration of effective perfusion ultimately depends on the recovery of necrotic areas (ie, removal of dead cells, granulation tissue formation, etc.), the prevention of excessive inflammatory and procoagulant response(s), the restoration of microcirculation (angiogenesis), and the prevention of further growth of atherosclerotic plaque (and their stability).

Monocytes are actively involved in all of these processes, and the aim of this overview is to summarize the available data on the involvement of monocytes in the pathological processes related to acute coronary syndrome (ACS). In this article, we put an emphasis on circulating monocytes rather than on their follow-on cells, the macrophages. The role of the latter (ie, macrophages) in ACS has recently been reviewed. A brief overview of monocyte counts in total blood from patients presenting with acute MI is provided in the supplemental Appendix.

Monocyte Activation

Before their involvement in the pathogenesis of ACS, monocytes are undergoing phenotypic transformation, leading to their activation. CD14, which is monocyte endotoxin receptor—together with toll-like receptors (TLR)—bind lipopolysaccharides (LPS) evoking monocyte activation, and the interaction between leukocytes and endothelium results in an inflammatory cytokine cascade (Figure). This process is further enhanced by high levels of C-reactive protein (CRP) or heat shock proteins seen in patients with ACS.

TLRs appear to be especially important for monocyte activation in ACS. Receptors of the TLR family recognize host-derived molecules released from injured tissues and initiate production of cytokines by different cells including monocytes. Stimulation of TLRs activates the proinflammatory transcription factor nuclear factor κB (NFκB) and the mitogen-activated protein kinase pathway, resulting in the production of cytokines that augment local inflammation. TLR1, TLR2, and TLR4 are upregulated in the endothelium and in areas infiltrated with inflammatory cells (ie, macrophages) within atherosclerotic plaques.

However, circulating monocytes also express TLR4, and their number is significantly elevated in patients with ACS. Indeed, circulating TLR4/CD14+ monocytes are ~2.5-fold increased in ACS patients, and the density of CD14 on the monocyte surface is much higher in patients with myocardial necrosis. Monocytic TLR4 overexpression in acute MI, as demonstrated both in the circulation and on ruptured plaque, has been associated with high levels of IL-6 and tumor...
necrosis factor-α (TNF-α). These markers remained elevated for at least 2 weeks after MI onset and have been associated with the development of heart failure. In some (but not all) studies, the CD14 gene polymorphism has been associated with a history of ACS or MI, indicating its potential role in genetic predisposition to the development of ACS and atheromatous plaque vulnerability (supplemental Table II).

In the PROVE IT-TIMI 22 trial, neopterin (a soluble marker of monocyte activation) has been shown to be increased at 7 days and at 4 months after ACS and identified patients at long-term risk of death or recurrent acute coronary events. Of note, Chlamydia pneumoniae was detected in CD14+ cells in more than a quarter of ACS patients, perhaps providing a potential bridge between an infectious agent and plaque destabilization, via monocyte activation.

Monocyte–Endothelium and Monocyte–Myocardial Interactions

On being activated, monocytes modify their phenotype, thus enhancing their interaction with endothelial cells and ability to damage cardiac tissue. Increased monocyte expression of Mac-1 (CD11b/CD18) receptor, lymphocyte function associated antigen-1, and very late after activation antigen-4 promote monocyte attachment to the endothelium. Monocyte-associated levels of intercellular adhesion molecule (ICAM-1), vascular cell adhesion molecule (VCAM-1), and L-selectin are also elevated from the early stages of ACS, either with or without myocardial necrosis being present. Also, monocytes possess receptors to localize at sites of injured myocardium. The ACS-related upregulation of monocyte fibronectin receptor VLA-5 may be involved in their migration to tissue fibronectin, the latter being an important component of cardiac extracellular matrix.

Injured heart muscle also promotes monocyte recruitment. Indeed, acute MI is associated with the rapid induction of mononuclear cell chemoattractants (such as monocyte chemotactic protein [MCP-1] and macrophage colony-stimulating factor [M-CSF]) that promote monocyte infiltration into the injured area, as well as monocyte differentiation to macrophages and proliferation of the latter, all critical processes for effective healing of the infarct area.

MCP-1 (gene name CCL2, receptor gene name CCR2) is the most important chemokine that regulates migration and infiltration of monocytes/macrophages. Ischemia rapidly stimulates MCP-positive macrophage infiltration of injured

Figure. Monocytes in acute coronary syndromes. LFAA indicates lymphocyte function associated antigen; VLAAA, very late after activation antigen; PPAR, peroxisome proliferator-activated receptor; COX, cyclooxigenase; MG-CSF, macrophage granulocyte colony-stimulating factor; FSAP, factor VII activating protease.
area directly or via M-CSF expression by mature cardiac resident macrophages.\textsuperscript{19} MCP-1 production by cultured human cardiac cells has been shown to be upregulated by inflammatory cytokines and downregulated by hypoxia.\textsuperscript{20} Cardiac overexpression of MCP-1 induces macrophage infiltration, neovascularization, expression of a wide range of cytokines and chemokines, and the accumulation of cardiac myofibroblasts, thereby affecting left ventricular (LV) remodelling.\textsuperscript{20}

Of note, although circulating monocytes were shown to express high plasma levels of MCP-1 in ACS, this chemokine is similar to inflammatory cytokines and is produced by different cell types within the heart and the arterial wall, including endothelial cells, smooth muscle cells, cardiomyocytes, and macrophages.\textsuperscript{21} Together these cells orchestrate local mobilization of monocytes in reparative processes in response to the ischemia and inflammation which is seen in ACS.\textsuperscript{22}

Plasma MCP-1 levels increase as early as 3 hours after the onset of chest pain, reach their maximum at 24 hours, and remain elevated for at least 7 days.\textsuperscript{23} Interestingly, the majority of studies on MCP-1 genetic polymorphism failed to find any association with the risk of MI (supplemental Table III). However, in the Framingham Heart Study Offspring Cohort, the MCP-1 to 2578G allele was significantly related to a higher prevalence of MI (adjusted Odds Ratio 2.0).\textsuperscript{24} Also, stress-induced expression of MCP-1 contributes significantly to the development of coronary collaterals during the early phase of acute MI.\textsuperscript{25} Nonetheless, excessive MCP-1 production may have adverse effects.\textsuperscript{26,27} Interestingly, MCP-1 levels appear to have little prognostic importance in patients with stable CAD.\textsuperscript{28}

MCP-1 may be potential target for intervention, but data from preclinical data have been controversial. In experimental studies, a genetically determined lack of MCP-1 synthesis or anti–MCP-1 therapy is associated with more favorable myocardial remodeling, better survival and contractility preservation, attenuated interstitial fibrosis and reduced infarct size, but also with delayed replacement of injured cardiomyocytes with granulation tissue and defective macrophage differentiation.\textsuperscript{29,30} In contrast, two rodent studies show that cardiac MCP-1 overexpression or myocardial MCP-1 injection reduced infarct area and scar formation and prevented LV dysfunction after MI.\textsuperscript{21,31} Of note, MCP-1 treatment stimulates neovascularization independent from bone marrow EPC involvement.\textsuperscript{30} Thus, the time and extent of MCP-1 availability may be of importance.

**Monocytes and Inflammation**

Monocytes are actively involved in triggering the inflammatory cascade in ACS. Activated monocytes promote the synthesis of proinflammatory molecules, such as IL-6 and TNF-α, partly mediated by TLR4 stimulation and Mac-1 expression—as discussed above.\textsuperscript{6} The antiinflammatory cytokine IL-10 is also upregulated in response to TNF-α in ACS, suggesting a control mechanism for inflammation.\textsuperscript{31} Catecholamines are directly involved in the regulation of IL-10 expression in monocytes, but not in T-cells, after acute stressful conditions.\textsuperscript{31} Furthermore, circulating monocytes in ACS produce equal amounts of TNF-α, but less IL-10, after stimulation with LPS in vitro as compared with healthy controls.\textsuperscript{32} Thus, the production of proinflammatory cytokines is not counterbalanced by antiinflammatory cytokines such as IL-10.

Local inflammation potentiated by overexpression of inflammatory factors by leukocytes stimulates excessive transendothelial migration of monocytes from the peripheral blood into the tissues. This process is regulated by bidirectional signaling in both leukocytes and vascular endothelium with major role of cAMP pathway.\textsuperscript{33} cAMP-mediated signaling regulates a wide range of cellular processes, including differentiation, secretion, regulation of cell shape, cytoskeletal remodelling, apoptosis, as well as adhesion and migration of leukocytes to tissues.\textsuperscript{34} In ACS, excessive stimulation of catecholamines, which are potent cyclic adenylate cyclase stimulators, further amplify cAMP production and cAMP-mediated monocyte migration to the atherosclerotic plaque, and modify their secretion of cytokines and differentiation into tissue macrophages.

**Plaque Destabilization and Monocytes**

Monocytes are involved in the destabilization of atherosclerotic plaques by their production of MMPs. Indeed, catecholamines potentiate LPS-induced synthesis of MMP-1 and MMP-9 in circulating monocytes and monocyte-derived macrophages.\textsuperscript{35} Oxidized LDL also stimulates monocyte expression of the urokinase receptor and consequent urokinase-mediated MMP-9 generation.\textsuperscript{36} The scavenger receptors type A (SR-A) and a chemokine, CXCL 16, are responsible for the uptake of oxidized LDL and phosphatidylyserine and transforming the macrophage into a foam cell.

In other studies, increased monocyte expression of extracellular MMP inducer (EMMPI) and cyclooxygenase-2 enhance the production of MMP-1 and MMP-9 in acute MI.\textsuperscript{37} In animal models of acute MI, strong monocyte myeloperoxidase activity correlates with progressive LV dilation and LV function impairment.\textsuperscript{38} Also, human monocytes stimulated with TNF-α release angiotensin II, which mediates an increase in MMP-1 synthesis.\textsuperscript{39}

Macrophage/foam cells produce cytokines that activate neighboring smooth muscle cells, resulting in extracellular matrix formation, fibrosis, and plaque instability. Gene expression profiles revealed that among the immune response factors and the receptor activity markers, SR-A was the most markedly increased in the acute phase of ACS.\textsuperscript{40} Recurrence of cardiovascular events was significantly lower in the “low SR-A” group compared to patients in the “high SR-A” group.\textsuperscript{40} The number of SR-A-positive monocytes is much higher among patients with ACS compared to those with chronic coronary disease, and this was associated with higher rate of residual mural thrombus in acute MI patients.\textsuperscript{41}

**Thrombosis**

Patients with ACS and MI survivors have significantly higher monocyte procoagulant activity, which is partly explained by monocyte upregulation of coagulation factor X and tissue factor (TF).\textsuperscript{42,43} IL-6 and CRP-stimulated monocyte Mac-1 expression catalyzes the conversion of factor X to Xa.\textsuperscript{43} Also,
monocyte expression of factor VII activating protease in vulnerable atherosclerotic plaque is increased in ACS being induced by proinflammatory mediators.44 Furthermore, monocyte-derived microparticles abundant in ACS enhance monocyte TF expression in vitro.45

Analysis of TF gene polymorphisms in FRISC-II trial reveal that the CG haplotype in 1812 C>T and 5466 A>G alleles was associated with a 3-fold increased risk of death in ACS.46 Of note, basal TF activity was significantly lower among 5466 AG carriers, whereas the increase in monocyte TF activity in response to LPS stimulation was significantly stronger in such subjects.47

Platelet-monocyte interactions have an important role in the procoagulant state typically seen in ACS. Binding of MI monocyte EMMPRI to platelets fosters platelet degranulation and related to increased monocyte CD40L expression observed in these patients.46,48 Degranulated platelets very rapidly form circulating aggregates with monocytes, the so-called monocyte-platelet aggregates (MPA).49 Circulating MPAs have been found to be a more sensitive marker of in vivo platelet activation than platelet surface P-selectin.50

Different mechanisms of platelet–leukocyte binding have been demonstrated in ACS, for example, via P-selectin glycoprotein ligand-1, P-selectin and calcium-independent mechanisms.51,52 Circulating MPA can be an early marker of acute MI and can be detected in the whole blood by flow cytometry as early as 4 hours after chest pain onset and before the increase in creatine kinase isoenzyme levels.53 MPAs are also increased in patients with NSTE-ACS, especially in those with troponin elevation.50,51 Interactions with platelets stimulate monocyte expression of Mac-1, NFκB activation, and increased production of IL-1β, IL-6, IL-8, TF; indeed, MCP-1 changes were suggested to be an important factor of microvascular refill abnormalities after reperfusion.54 Enhanced generation of MPA is associated with high risk of future cardiovascular events.55

**Monocyte-Derived EPCs**

Human monocytes include a population of cells that can acquire an endothelial cell phenotype in culture. Moreover, cultures of so-called “early” EPCs mainly comprise T cells and monocytes, and their formation is strictly dependent on the presence of monocytes.56 Monocytes cultured under angiogenic conditions lose CD14/CD45 and display an endothelial phenotype.57 Indeed, human bone marrow also includes CD14+CD34− cells capable to improve reendothelialization after carotid balloon injury in animals.58 These monocyte lineage cells express endothelium-specific markers (Tie2, CD31, VE-cadherin, and endoglin) and adhere to injured endothelium via MCP-1 dependant mechanism in vivo or in vitro.57

In an experimental study, monocytes also include subpopulations of multipotent cells capable of in vitro differentiation into various somatic cell types.58 These cells, but not the nonmodulated monocytes, were able to successfully restore LV function after experimental MI in animals.59

The number of circulating CD14+/KDR+ cells has been found to be increased in acute MI. CD14+/KDR+ but not CD14+/KDR− cells stimulated the organization of human microvascular endothelial cells into capillary-like structures.60 Human activated macrophages that are delivered to rats early after MI accelerates vascularization, tissue repair, and improves cardiac remodeling and function.61 In mice, M-CSF reduces the infarct area and improves LV remodeling after MI through the recruitment of CXCR4+ cells into the infarcted myocardium.62

The role of other monocyte subset populations in ACS is discussed in the supplemental materials. The impact of monocytes on ACS development and recovery makes them a potential target for pharmaceutical treatment, as highlighted in supplemental Table IV.

**Conclusion**

Monocytes appear to be actively involved in all key stages of ACS. In view of recent findings, monocytes may be considered not only as a classical element of innate immunity, but also as an important part of coagulates system and potentially as an instrument of regenerative forces of human body. However, further studies are clearly needed to clarify the precise role of monocytes in ACS, as well as potential novel targets for treatments.

**Sources of Funding**

Eduard Shantsila is funded by a research grant by the Heart Failure Association of the European Society of Cardiology. We acknowledge the support of the Peel Medical Research Trust and Heart Research UK for the Haemostasis Thrombosis and Vascular Biology Unit.

**Disclosures**

None.

**References**

10. Ishikawa Y, Satoh M, Itoh T, Minami Y, Takahashi Y, Akamura M. Local expression of Toll-like receptor 4 at the site of ruptured plaques in


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Arterioscler Thromb Vasc Biol. 2009;29:1433-1438; originally published online February 19, 2009;
doi: 10.1161/ATVBAHA.108.180513

Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1079-5642. Online ISSN: 1524-4636

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://atvb.ahajournals.org/content/29/10/1433

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Supplement Material

Monocyte subsets

In humans, CD14+/CD16- monocytes comprise the major subset in the circulation, whereas CD14\textsuperscript{low}/CD16\textsuperscript{+} monocytes are typically infrequent (less than 15%).\textsuperscript{1} Although CD14\textsuperscript{low}/CD16\textsuperscript{+} monocytes appear to be ‘follow-on’ cells from the CD14\textsuperscript{+}/CD16\textsuperscript{-} monocytes, these two subsets have been shown to have different functional roles (for example, in inflammatory and infection disorders).\textsuperscript{2} Indeed, macrophages in atherosclerotic plaques express CD16 and the number of CD14\textsuperscript{low}/CD16\textsuperscript{+} monocytes is significantly increased in patients with hypercholesterolemia and stable CAD.\textsuperscript{3-5}

Recent animal studies strongly indicate a difference in the role of different functional monocyte subpopulations in experimental ACS, which may contribute in specific ways to myocardial ischemic injury or recovery. In mice, Ly-6C\textsuperscript{low} monocytes (the equivalent of human CD14\textsuperscript{low}/CD16\textsuperscript{+} cells) play an important role in replenishing the damaged local macrophage pool, for example, in the lung.\textsuperscript{6}

More recently, two distinct phases of monocyte participation after MI were identified in the mouse.\textsuperscript{6} Ly-6C\textsuperscript{high} monocytes (the equivalent of human CD14\textsuperscript{+}/CD16\textsuperscript{-} cells) dominate at early phase of MI and exhibit phagocytic, proteolytic and inflammatory functions. In contrast, Ly-6C\textsuperscript{low} monocytes predominate later on, and have attenuated inflammatory properties, and express vascular endothelial growth factor. Consequently, Ly-6C\textsuperscript{high} monocytes digest damaged tissue, whereas Ly-6C\textsuperscript{low}
monocytes promote healing via myofibroblast accumulation, angiogenesis and the deposition of collagen. Indeed, experimental MI models in atherosclerotic mice with chronic Ly-6C\textsuperscript{high} monocytosis results in impaired healing, thus underscoring the need for a more balanced and coordinated monocyte response.

**Treatment**

The significant impact of monocytes on ACS development and recovery makes them a potential target for pharmaceutical treatment. A limited number of studies are currently available on effects on drug therapy, most of which are routinely used for ACS treatment, on monocyte activity (Table 4).

**Anticoagulants.**

Abciximab (but not heparin) reduces platelet mass attached to monocytes in acute MI patients through the reduction of Mac-1 expression but did not affect the number of MPA.\textsuperscript{7} Combination of reteplase and abciximab is much more effective in MPA reduction than reteplase alone.\textsuperscript{8} Implantation of heparin-coated stents in ACS accelerates platelet-leukocyte aggregates level normalisation compared to balloon angioplasty alone.\textsuperscript{9}

**ACE inhibitors and angiotensin II receptor antagonists**

Captopril, idrapril, fosinopril and losartan decreases monocyte TF expression in vitro.\textsuperscript{10} In a small randomized, double-blind, placebo-controlled study 4 weeks treatment with enalapril (5 mg daily) significantly reduced MCP-1 levels in MI
patients.\textsuperscript{11} However, no effect of perindopril or candesartan on MCP-1 levels was found in acute MI.\textsuperscript{12}

\textit{Antiplatelet drugs.}

Both loading dose (300mg) and continuous administration of clopidogrel 75 mg/day as maintenance dose decreases MPA numbers in ACS.\textsuperscript{13}

\textit{Statins.}

Atorvastatin reduced MCP-1 levels in ACS and monocyte cyclooxygenase-2 expression AMI patients.\textsuperscript{14,15} Another statin, cerivastatin was able to decrease expression of urokinase receptors on monocytes.\textsuperscript{16}

\textit{Other drugs.}

In \textit{in vitro} studies celecoxib dramatically reduced monocyte secretion of IL-6 and MMP-9 and dobutamine successfully inhibited LPS-induced production of MCP-1.\textsuperscript{17,18} In animal MI models, eplerenone effectively prevents LV dilation and improved LV function via mineralocorticoid receptor blockade.\textsuperscript{19}

**References**


46. Kim MP, Zhou M, Wahl LM. Angiotensin II increases human monocyte matrix metalloproteinase-1 through the AT2 receptor and prostaglandin E2:


52. Unkelbach K, Gardemann A, Kostrzewa M, Philipp M, Tillmanns H, Haberbosch W. A new promoter polymorphism in the gene of lipopolysaccharide receptor CD14 is associated with expired myocardial


Table 1. Changes in the expression of biologically active molecules by monocytes in ACS

<table>
<thead>
<tr>
<th>Changes observed in ACS</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Expression of surface receptors</strong></td>
<td></td>
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<tr>
<td>Lipopolysaccharid receptors (CD14)</td>
<td>Increased expression</td>
</tr>
<tr>
<td>Toll-like receptor 4</td>
<td>Increased expression</td>
</tr>
<tr>
<td>Mac-1 (CD11b/CD18) receptor, lymphocyte function associated antigen-1</td>
<td>Increased expression</td>
</tr>
<tr>
<td><strong>Adhesion molecules</strong></td>
<td></td>
</tr>
<tr>
<td>ICAM, VCAM, L-selectin</td>
<td>Increased synthesis</td>
</tr>
<tr>
<td><strong>Cytokines related to inflammation</strong></td>
<td></td>
</tr>
<tr>
<td>TNF-α, IL-1β, IL-6, IL-12</td>
<td>Increased production</td>
</tr>
<tr>
<td>IL-10</td>
<td>Production is increased by catecholamine stimulation, reduced production following lipopolysaccharid stimulation</td>
</tr>
<tr>
<td><strong>Extracellular matrix degradation</strong></td>
<td></td>
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<tr>
<td>MMP-1, MMP-9</td>
<td>Increased production</td>
</tr>
<tr>
<td>Extracellular MMP inducer</td>
<td>Increased production</td>
</tr>
<tr>
<td><strong>Prothrombotic markers</strong></td>
<td></td>
</tr>
<tr>
<td>Factor X, tissue factor</td>
<td>Increased synthesis</td>
</tr>
<tr>
<td>Factor VII activating protease</td>
<td>Increased synthesis</td>
</tr>
<tr>
<td>Tissue factor-expressing</td>
<td>Increased production</td>
</tr>
<tr>
<td>monocyte-derived microparticles</td>
<td>CD40 ligand</td>
</tr>
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<tr>
<td>Monocyte-platelet aggregates</td>
<td>Increased formation</td>
</tr>
</tbody>
</table>

**Leukocyte mobilisation**

| Monocyte chemoattractant protein-1 | Increased production | 44, 45 |

**Vascular and cardiac remodelling**

| Angiotensin II | Increased following stimulation by TNF-α | 46 |

Table 2. Studies on CD14 gene polymorphism.

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Polymorphism analysed</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hubacek et al&lt;sup&gt;47&lt;/sup&gt;</td>
<td>178 patients with MI and 135 control subjects.</td>
<td>-260 C/T</td>
<td>The frequency of the T allele was higher in MI patients, with higher density of the CD14 receptor the T/T homozygotes.</td>
</tr>
<tr>
<td>Shimada et al&lt;sup&gt;48&lt;/sup&gt;</td>
<td>81 MI patients, 43 CAD patients, 83 healthy controls</td>
<td>-260 C/T</td>
<td>The frequencies of T allele and T/T homozygotes in MI patients were higher than in controls and in patients with angina without prior AMI.</td>
</tr>
<tr>
<td>Heessen et al&lt;sup&gt;49&lt;/sup&gt;</td>
<td>95 healthy blood donors</td>
<td>-260 C/T</td>
<td>No differences in CD14 density and soluble CD14 levels.</td>
</tr>
<tr>
<td>Arroyo-Espliguero et al&lt;sup&gt;50&lt;/sup&gt;</td>
<td>194 ACS survivors, 140 CAD patients without ACS history, 94 patients with normal coronary artery</td>
<td>-260 C/T</td>
<td>Patients with a prior ACS had higher frequency of the T/T genotype than CAD patients without prior ACS. No differences between CAD patients without prior ACS and controls.</td>
</tr>
<tr>
<td>Longobardo et al&lt;sup&gt;51&lt;/sup&gt;</td>
<td>213 MI survivors</td>
<td>-260 C/T</td>
<td>No association with AMI presence</td>
</tr>
<tr>
<td>Study</td>
<td>Participants</td>
<td>Genotype</td>
<td>Results</td>
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<tr>
<td>-------------------------------</td>
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</tr>
<tr>
<td>Agema et al (REGRESS trial)⁵</td>
<td>213 healthy controls</td>
<td>-159 C/T</td>
<td>No association with CAD severity</td>
</tr>
<tr>
<td>Unkelbach et al⁵²</td>
<td>759 patients with CAD</td>
<td>-159 C/T</td>
<td>No association with MI or CAD in the whole cohort. In low coronary risk patients (normotensive nonsmokers) increased risk for MI T allele homozygotes (OR 1.6).</td>
</tr>
<tr>
<td>Koch et al⁵³</td>
<td>2228 patients after diagnostic coronary angiography</td>
<td>-159 C/T</td>
<td>Gen polymorphism was not associated with CAD or MI.</td>
</tr>
<tr>
<td>Koch et al⁵³</td>
<td>793 MI patients, 998 CAD patients, 340 healthy controls</td>
<td>-159 C/T</td>
<td>No differences in the first MI age or the number of cardiovascular risk factors.</td>
</tr>
</tbody>
</table>
Table 3. Studies on MCP-1 gene polymorphism.

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Polymorphism analysed</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iwai et al&lt;sup&gt;55&lt;/sup&gt;</td>
<td>2,266 subjects, including 34 MI survivors</td>
<td>-2138 A/T</td>
<td>No significant association with MI or atherosclerosis</td>
</tr>
<tr>
<td>Jemaa et al&lt;sup&gt;56&lt;/sup&gt;</td>
<td>319 MI patients, 467 healthy controls</td>
<td>-2518 G/A</td>
<td>Patients with MI had significantly higher frequency of the AG+GG genotypes compared to controls.</td>
</tr>
<tr>
<td>McDermott et al&lt;sup&gt;57&lt;/sup&gt; (Framingham Heart Study Offspring Cohort)</td>
<td>1797 subjects</td>
<td>-2518 G/A</td>
<td>The MCP-1-2578G allele was associated with higher serum MCP-1 levels and higher MI prevalence (adjusted odds ratio, 2.0).</td>
</tr>
<tr>
<td>Bjarnadottir et al&lt;sup&gt;58&lt;/sup&gt;</td>
<td>460 MI survivors, 1842 disease free controls</td>
<td>-2518 G/A, -2076 A/T plus -190 G/A polymorphism of CCR2 gene</td>
<td>No difference in the frequencies of any of the polymorphisms studied between the cases and the controls.</td>
</tr>
<tr>
<td>Cermakova et al&lt;sup&gt;59&lt;/sup&gt;</td>
<td>139 MI patients, 359 healthy controls</td>
<td>-2518 G/A</td>
<td>No relationship was observed between circulating MCP-1 levels and carriage of the G allele.</td>
</tr>
</tbody>
</table>
Table 4. Effects of pharmaceutical treatment on monocytes.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Species</th>
<th>Disorder/Model</th>
<th>Effects on monocytes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abciximab</td>
<td>Human</td>
<td>MI</td>
<td>Reduced Mac-1 expression and platelet mass attached to monocytes; no effect on MPA number.</td>
</tr>
<tr>
<td>Reteplase and abciximab</td>
<td>Human</td>
<td>MI</td>
<td>Reduced MPA number more effectively that reteplase alone.</td>
</tr>
<tr>
<td>Heparin-coated stents</td>
<td>Human</td>
<td>ACS</td>
<td>Restored MPA quicker compared to angioplasty alones.</td>
</tr>
<tr>
<td>Kaptopril, idrapril, fosinopril, losartan</td>
<td>Human</td>
<td>Healthy volunteers</td>
<td>Decreased monocyte TF expression.</td>
</tr>
<tr>
<td>Enalapril</td>
<td>Human</td>
<td>MI</td>
<td>Reduced MCP-1 levels.</td>
</tr>
<tr>
<td>Perindopril, candesartan</td>
<td>Human</td>
<td>MI</td>
<td>No effects on MCP-1 levels.</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>Human</td>
<td>ACS</td>
<td>Decreased MPA number.</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>Human</td>
<td>ACS</td>
<td>Reduced MCP-1 levels.</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>Human</td>
<td>MI</td>
<td>Reduced monocyte cyclooxigenese-2.</td>
</tr>
<tr>
<td>Cerivastatin</td>
<td>Human</td>
<td>Healthy volunteers</td>
<td>Decreased expression of urokinase receptor on monocytes.</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>Human</td>
<td>MI</td>
<td>Reduced monocyte secretion of IL-6 and MMP-9.</td>
</tr>
<tr>
<td>Dobutamine(^\text{18})</td>
<td>Human Monocyte culture</td>
<td>Inhibited LPS-induced production of MCP-1.</td>
<td></td>
</tr>
<tr>
<td>-------------------------</td>
<td>------------------------</td>
<td>-------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Eplerenone(^\text{19})</td>
<td>Rat MI</td>
<td>Prevented LV dilation and improved LV function via mineralocorticoid receptor blockade.</td>
<td></td>
</tr>
</tbody>
</table>