Monocyte Chemoattractant Protein-1/CCL2 as a Biomarker in Acute Coronary Syndromes

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The CC chemokine monocyte chemoattractant protein (MCP)-1/CCL2 is involved in the formation, progression, and destabilization of atheromatous plaques and plays an essential role in postinfarction remodeling. These properties generated significant interest in the potential significance of MCP-1 as a biomarker in acute coronary syndromes (ACS). Emerging evidence suggests that MCP-1 plasma levels have prognostic value in the acute and chronic phase following ACS, providing information independent of standard clinical variables. The mechanisms responsible for adverse prognosis in patients with elevated plasma MCP-1 following ACS remain unknown. High plasma MCP-1 levels may reflect a higher burden of atherosclerotic disease, may exert prothrombotic effects resulting in recurrent coronary events, or may identify patients who mount a more intense cardiac inflammatory reaction following a coronary event, resulting in enhanced adverse remodeling. Beyond its prognostic significance, the MCP-1 axis may be an attractive target for therapy in patients with ACS.

Introduction

Recent advances in cardiovascular research have provided new insight into the processes involved in the pathogenesis of acute coronary syndromes (ACS). Extensive evidence implicates inflammatory mediators in the development of atherogenesis. In addition, inflammation appears to play a fundamental role in the pathogenesis of plaque rupture. Earlier studies suggested that local inflammation results in rupture of a single vulnerable plaque, leading to coronary thrombosis. More recent evidence supported the emerging concept of the "vulnerable patient," suggesting that unstable coronary syndromes are associated with widespread inflammatory activation of the coronary tree [1,2]. Thus, both researchers and clinicians have turned to biochemical markers of inflammation as possible noninvasive indicators of the risk of recurrent cardiovascular events following an ACS and as predictors of the success of therapeutic interventions [3].

High-sensitivity C-reactive protein (hsCRP), the prototypical inflammatory biomarker, seems to provide important prognostic information in ACS. In patients with unstable angina or non–Q-wave myocardial infarction enrolled in the Thrombolysis in Myocardial Infarction (TIMI) 11A trial [4], elevated CRP at presentation correlated with 14-day mortality, even in patients with a negative rapid cardiac troponin T assay. In addition, persistent elevation of hsCRP 30 days following an ACS was associated with a significantly increased 2-year mortality rate in the Aggrastat-to-Zocor (A to Z) trial [5•]. Patients treated with more aggressive statin therapy were more likely to achieve lower levels of hsCRP. However, although CRP is a reliable marker of inflammation, several other immune and inflammatory mediators are critically involved in the pathogenesis of ACS and may serve as new biomarkers, providing additional diagnostic and prognostic information. These novel molecular markers may serve as a window into the underlying pathophysiologic mechanisms of coronary atherothrombotic disease and may guide a more individualized treatment approach.

The Chemokines

The chemokines are a family of small chemotactic cytokines with molecular weights in the range of 8 to 14 kDa and a strikingly similar tertiary structure. There are approximately 50 human chemokines, which can be classified into CC, CXC, C, or CX3C subfamilies based on the number of amino acids between the first two of the four conserved cysteine residues that characterize chemokine structure. From a functional standpoint, chemokines can be divided broadly into two categories: 1) homeostatic chemokines that are constitutively expressed in certain tissues and may be responsible for basal leukocyte trafficking and formation of the fundamental architecture of lymphoid organs, and 2) inducible chemokines that are strongly upregulated by inflammatory or immune stimuli and actively participate in

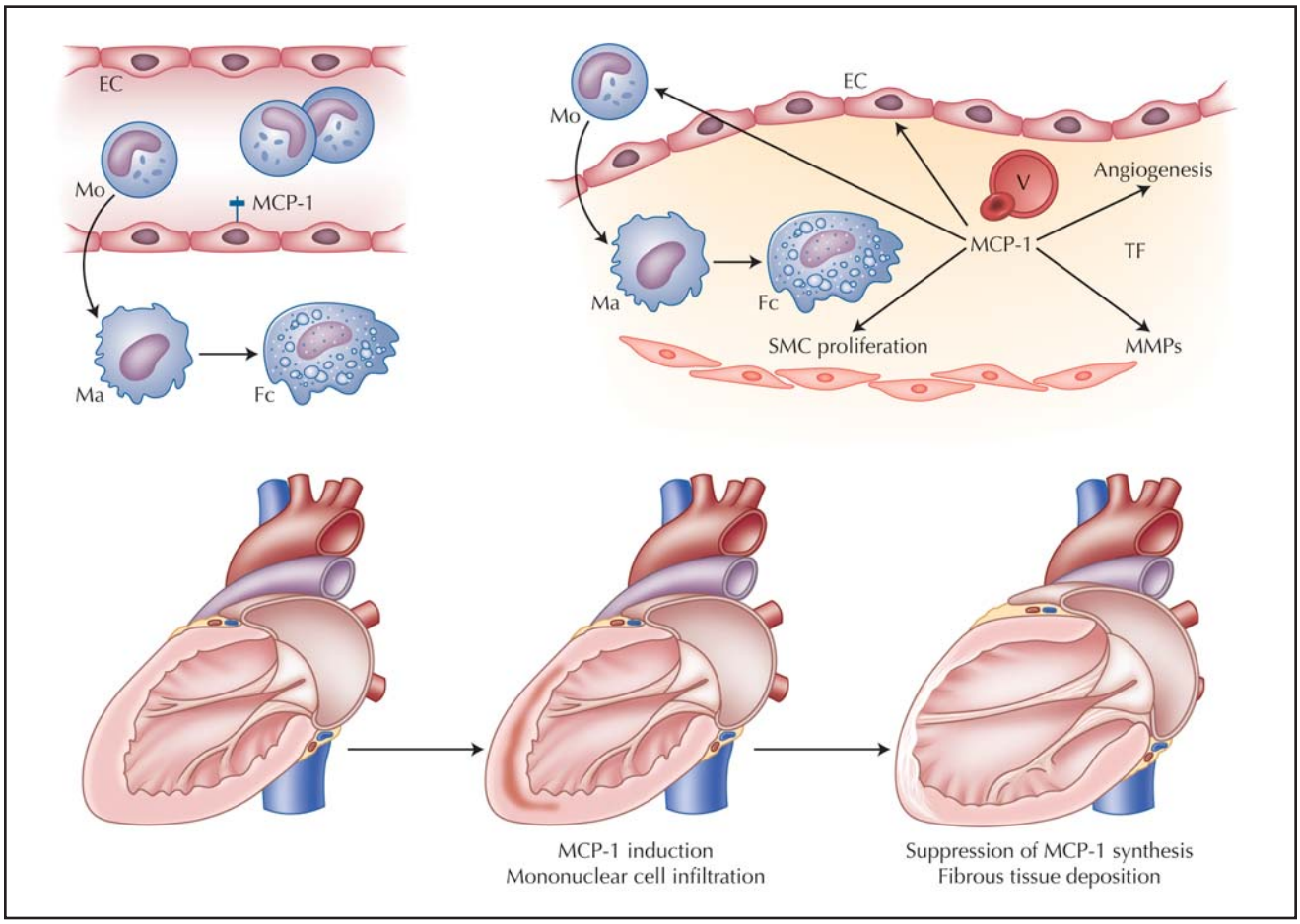

Figure 1. The role of monocyte chemoattractant protein (MCP)-1 in atherothrombotic disease and myocardial infarction. MCP-1 is markedly induced in early atherosclerotic lesions and is immobilized on the luminal surface of the endothelium through binding with proteoglycans. Interactions between MCP-1 and its receptor CCR2, expressed on mononuclear cells (Mo), mediate Mo recruitment into the subendothelial space. Monocytes differentiate into macrophages (Ma) and ingest lipids to form foam cells (Fc). MCP-1 is involved in Fc formation, one of the earliest manifestations of atherosclerosis (*upper left*). Enhanced expression of MCP-1 in the vascular wall may contribute to progression of atherosclerotic disease through Fc activation, stimulation of smooth muscle cell (SMC) proliferation, and induction of plaque neovascularization. MCP-1 may also induce matrix metalloproteinase (MMP) synthesis, promoting matrix degradation and plaque disruption. It is also capable of upregulating tissue factor (TF) expression by exerting procoagulant effects (*upper right*). MCP-1 is also involved in infarct healing and cardiac remodeling. During the proinflammatory phase of healing, MCP-1 is upregulated in the infarcted myocardium and mediates Mo recruitment. As the infarct heals, MCP-1 synthesis is suppressed, leading to resolution of inflammation and formation of a scar. Prolonged increase of plasma MCP-1 levels following acute coronary syndrome may identify patients exhibiting an enhanced inflammatory response in the healing myocardium. Timely repression of MCP-1 synthesis is crucial for optimal healing; sustained inflammation may result in extensive matrix degradation and adverse remodeling of the infarcted ventricle. EC—endothelial cell.

the inflammatory reactions by inducing leukocyte recruitment [6]. Although this generalization has been challenged by studies demonstrating that certain chemokines felt to be homeostatic (such as SDF-1) [7] are inducible upon immune activation, it offers valuable insight into the role of members of the chemokine family in pathologic states. Extensive evidence suggests that both CC and CXC chemokines are induced in human atherosclerotic lesions and may play a role in atherogenesis and plaque destabilization.

Monocyte Chemoattractant Protein-1/CCL2: An Essential Mediator in the Pathogenesis of Atherosclerosis

Monocyte chemoattractant protein (MCP)-1, the most thoroughly characterized CC chemokine, was identified as a monocyte-specific chemoattractant that was later demonstrated to attract T lymphocytes and natural killer cells but not neutrophils. Enhanced expression of MCP-1 was demonstrated in a variety of pathologic conditions associated with inflammation and mononuclear cell infiltration. Extensive experimental evidence suggests that MCP-1 is highly expressed in atherosclerotic plaques [8] and mediates macrophage recruitment in the atheromatous lesion (Fig. 1). Fatty streaks, the hallmark of early atherosclerotic disease, are composed of lipid-laden macrophages termed foam cells. Oxidized lipids mediate foam cell formation and have long been implicated as important mediators of atherosclerosis. Minimally oxidized low-density lipoproteins (LDLs), but not native LDLs, induce MCP-1 production in vascular endothelial and smooth muscle cells [9]. MCP-1 is tethered to proteoglycans on

the luminal side of endothelial cells and interacts with its receptor, CCR2, which is expressed on rolling monocytes. This interaction initiates firm integrin-mediated adhesive interactions between monocytes and endothelial cells, ultimately resulting in leukocyte diapedesis into the subendothelium. After entering the subendothelial space monocytes differentiate into macrophages, where they continuously ingest lipid to become the foam cells of the fatty streak [10]. Studies using genetically targeted animals provided strong evidence that MCP-1 plays an essential role in the recruitment of macrophages in atheromatous lesions. Deletion of the MCP-1 gene in LDL receptor–deficient mice [11] and in animals overexpressing human apolipoprotein (apo) B [12] protects the animals from the development of diet-induced atherosclerosis, dramatically reducing macrophage recruitment in the aortic wall without altering lipoprotein metabolism. In addition, deletion of CCR2, the only functional MCP-1 receptor, attenuated macrophage accumulation in atherosclerotic lesions and protected apoE-null mice fed a high-fat [13] or a regular chow diet from developing atherosclerosis [14]. Furthermore, MCP-1 inhibition using transfection with an N-terminal deletion mutant of the MCP-1 gene markedly inhibited formation of new atherosclerotic plaques in hypercholesterolemic mice [15].

The potential role of MCP-1 in progression of atherosclerotic disease and plaque rupture is less established (Fig. 1). MCP-1 induces smooth muscle cell proliferation and may exert angiogenic effects [16], promoting neovessel formation in the plaque; these actions may lead to rapid progression of the lesion [17]. MCP-1 may also play a role in disruption of the atherosclerotic plaque by inducing matrix metalloproteinase expression and release [18]. In addition, MCP-1 may have procoagulant properties by inducing tissue factor synthesis and activity in smooth muscle cells [19]. Although direct proof of the in vivo significance of these mechanisms is lacking, an inhibitory antibody to MCP-1 and MCP-5 administered to apoE$^{-/-}$ mice induced a stable plaque phenotype with increased collagen content [20]. In addition, blockade of MCP-1 through gene therapy limited progression of preexisting lesions in the aortic root in hypercholesterolemic mice [21]. This approach also altered the composition of atherosclerotic plaques into a more stable phenotype, containing fewer macrophages and lymphocytes, less lipid cells, and more smooth muscle cells and collagen [21].

MCP-1 in cardiac injury and repair

In addition to its established role in the pathogenesis of atherosclerotic disease and its potential significance in disease progression and plaque rupture, MCP-1 is also critically involved in the healing response following an acute coronary event [22]. Myocardial infarction triggers a local inflammatory reaction that results in formation of a scar and is closely intertwined with remodeling of the infarcted ventricle (Fig. 1). MCP-1 expression is markedly but transiently induced in infarcted hearts [23,24] and critically regulates the healing response. In vitro studies using postischemic cardiac lymph node tissue collected during canine reperfused infarction suggested that MCP-1 may be a major factor responsible for mononuclear cell recruitment into the ischemic myocardium during the first 5 hours of reperfusion [25]. In addition, in a rat model of experimental myocardial infarction, administration of a neutralizing antibody to MCP-1 significantly reduced infarct size, decreasing adhesion molecule expression and macrophage infiltration [26]. Beyond its leukotactic actions, MCP-1 may have important effects on infarct healing mediated through its direct angiogenic effects on the vascular endothelium [16] or by modulation of fibroblast phenotype and activity [27].

In order to examine the role of endogenous MCP-1 in infarct healing, we [28] studied the effects of MCP-1 gene disruption and antibody neutralization in a mouse model of reperfused myocardial infarction [28]. MCP-1$^{-/-}$ mice had decreased and delayed macrophage infiltration in the healing infarct and demonstrated delayed replacement of injured cardiomyocytes with granulation tissue. MCP-1$^{-/-}$ infarcts had decreased mRNA expression of the cytokines tumor necrosis factor-α, interleukin-1β, transforming growth factor-β, and interleukin-10, and they demonstrated defective macrophage differentiation. MCP-1 deficiency diminished myofibroblast accumulation but did not significantly affect infarct angiogenesis. Despite showing delayed phagocytotic removal of dead cardiomyocytes, MCP-1$^{-/-}$ mice had attenuated left ventricular remodeling, but similar infarct size, when compared with wild-type animals. MCP-1 antibody inhibition resulted in defects comparable with the pathologic findings noted in infarcted MCP-1$^{-/-}$ animals without an effect on macrophage recruitment [28]. Our study suggested that the role of MCP-1 extends beyond its monocyte chemoattractant effects: MCP-1 inhibition with a neutralizing antibody resulted in defects comparable with the pathologic findings noted in infarcted MCP-1$^{-/-}$ animals in the absence of impairment in monocyte recruitment. Suppression of inflammatory cytokine synthesis, decreased macrophage activation, selective recruitment of monocyte subsets with distinct properties, reduced MMP synthesis and activity, and diminished myofibroblast infiltration may be important mechanisms responsible for attenuated left ventricular remodeling in MCP-1$^{-/-}$ mice.

The key role of MCP-1 signaling in the pathogenesis of postinfarction remodeling was also suggested by experiments using mice with genetic disruption of CCR2, the primary receptor for MCP-1 [29]. CCR2-null mice had decreased infiltration with macrophages and exhibited attenuated ventricular dilation following myocardial infarction. CCR2 absence was associated with markedly decreased metalloproteinase expression and lower gelatinolytic activity in the infarcted ventricle. Attenuated matrix degradation may explain, at least in part, the protection from the development of adverse remodeling noted in CCR2-null animals.

Table 1. Studies supporting the prognostic value of MCP-1 in ACS

Study	Patients, *n*	Follow-up, *mo*	End points	Study design	Outcome
de Lemos et al. [39] (OPUS-TIMI 16)	2270 with ACS, 279 controls	10	All-cause death, nonfatal MI, recurrent ischemia requiring urgent revascularization congestive heart failure and composite (death or MI)	Prospective	Higher levels of MCP-1 were associated with death or MI
Kervinen et al. [40]	183	13	Recurrent unstable angina pectoris or MI, coronary revascularization (PCI or CABG), and cardiac death	Prospective	High MCP-1 levels predicted recurrent coronary event
de Lemos et al. [39] (A to Z trial)	4244	12	Death (primary) and secondary composite end points (death or MI; death, MI or heart failure; cardiovascular death, MI, readmission for ACS or stroke)	Prospective (serial MCP-1 measurements)	High MCP-1 levels predicted death and composite end points

A to Z—Aggrastat to Zocor; ACS—acute coronary syndrome; CABG—coronary artery bypass grafting; MCP—monocyte chemoattractant protein; MI—myocardial infarction; OPUS-TIMI—Oral Glycoprotein IIb/IIIa Inhibition with Orbofiban in Patients with Unstable Coronary Syndromes–Thrombolysis In Myocardial Infarction; PCI—percutaneous coronary intervention.

During the inflammatory stage of infarct healing, MCP-1 mediates macrophage recruitment and timely clearance of dead cells from the infarct; however, prolonged induction of the chemokine in the infarcted heart may result in extension of granulation tissue formation and adverse remodeling of the ventricle [30]. Thus, timely resolution of the inflammatory response following myocardial infarction is critical for optimal healing.

MCP-1 as a biomarker in ACS

Evidence suggests that MCP-1 may not be a clinically useful tool in diagnosis of subclinical atherosclerosis. In the Dallas Heart Study [31], MCP-1 plasma levels were associated with traditional cardiovascular risk factors and with coronary artery calcium. After adjustment for age, MCP-1 levels were no longer independently associated with subclinical atherosclerosis [31]. A few case-control studies examined the ability of MCP-1 levels to predict established cardiovascular disease. In the Atherosclerosis Risk in Communities (ARIC) study [32], patients with incident peripheral arterial disease had significantly higher plasma MCP-1 levels in comparison with control patients. However, the association between MCP-1 levels and peripheral arterial disease was no longer statistically significant when CRP was added to a model that included multiple inflammation-related variables. The limited value of plasma MCP-1 levels as a predictor of atherosclerotic disease, despite the marked activation of the MCP-1/CCR2 axis in the vascular wall, may reflect the immobilization of the chemokine on the luminal surface of endothelial cells. Binding to glycosaminoglycan chains of cell surface proteoglycans is essential for MCP-1 actions in vivo, ensuring high local concentrations of MCP-1 and providing directional signals for monocyte migration [33]. Selective induction and localization of MCP-1 in atheromatous plaques may not result in marked elevations of plasma MCP-1 levels.

The involvement of MCP-1 in atherothrombotic disease and in the pathogenesis of cardiac remodeling suggested that MCP-1 may be a promising biomarker for risk prediction in patients with coronary artery disease [34•,35]. Several small case-control studies indicated that plasma MCP-1 levels were highest among patients with ACS, intermediate among patients with stable coronary disease, and lowest among healthy controls [36,37]. Aukrust et al. [38] demonstrated that MCP-1 levels are increased in patients with unstable angina in comparison with gender and age-matched controls and to patients presenting with stable effort angina [38]. However, there was considerable overlap in MCP-1 levels between groups, indicating that MCP-1 will not be useful as a diagnostic marker in ACS.

Emerging evidence suggests that MCP-1 may have value as a prognostic marker in patients with ACS (Table 1). A substudy of the Oral Glycoprotein IIb/IIIa Inhibition with Orbofiban in Patients with Unstable Coronary Syndromes (OPUS-TIMI 16) trial [39] was the first to prospectively assess the value of MCP-1 as a prognostic biomarker in patients with ACS. In this study, 279 volunteers and 2270 patients were evaluated [39]. Assessment of MCP-1 levels was performed prior to initiation of treatment with the glycoprotein IIb/IIIa inhibitor, and the study population was divided in quartiles according to the levels of MCP-1 in serum. When compared with the first three quartiles, patients with MCP-1 levels above the 75th percentile (> 238 pg/mL, corresponding to the 90th percentile in the control population) exhibited a trend toward increased mortality during the 10-month follow-up period and were more likely to suffer death or myocardial infarction. The association remained after adjustment for several clinical (age, history of diabetes, hypertension, hypercholesterolemia, coronary disease, creatinine clearance, ST deviation) and biochemical (CRP and troponin I elevation) risk predictors. Although the findings supported the role of MCP-1

as a predictive biomarker in patients with ACS, the lack of serial measurements prevented determination of the optimal time point for measuring plasma levels.

The predictive value of MCP-1 plasma levels was supported by a smaller prospective study that enrolled an unselected population of patients with ischemic chest pain representing the whole clinical spectrum of ACS [40]. Blood samples were taken immediately after admission, and patients were followed for 13 months. Plasma MCP-1 level above the median (> 144 pg/mL) was a predictor of future coronary events (recurrent angina or acute infarction, coronary revascularization, or cardiac death). In addition, patients who died had the highest mean levels of MCP-1/CCL2 (355 ± 220 pg/mL), suggesting that the severity of a future event increased with increasing MCP-1 levels. Moreover, patients with an early event (7 days or earlier) had higher MCP-1/CCL2 blood levels compared with the ones that presented a nonfatal end point later (after 7 days).

Serial measurement of plasma MCP-1 levels may provide additional prognostic information in patients with ACS. A small study demonstrated a sustained increase in MCP-1 levels in patients with complicated myocardial infarction. During the first week of hospitalization, peak MCP-1 levels were higher in patients with infarction complicated by heart failure in comparison with patients with an uncomplicated course [41]. One month after the event, patients with severe left ventricular dysfunction (left ventricular ejection fraction < 35%) exhibited significantly higher plasma levels of MCP-1 (and several other CC chemokines) than patients with more preserved function (ejection fraction > 35%). A recent prospective study measured MCP-1 levels in a large population of patients with ACS enrolled in the A to Z trial and examined the prognostic value of serial measurement of MCP-1 levels at the time of enrollment to the Z phase (median 3.5 days after symptom onset) and at the 4-month and 12-month outpatient visits [42••]. The primary outcome was all-cause mortality. The secondary end points were myocardial infarction and the composites of death and myocardial infarction; death, myocardial infarction, and new or worsening hear failure; and the phase Z primary end point of cardiovascular death, myocardial infarction, readmission for ACS, and stroke. The study confirmed that baseline MCP-1 levels provide independent prognostic value in patients with ACS. The incidence of all primary and secondary end points increased across quartiles of baseline MCP-1 plasma levels. In addition, patients with baseline MCP-1 levels above the prespecified threshold of 238 pg/mL (based on the findings from the OPUS-TIMI 16 substudy [39]) were also at increased risk for death and for each of the secondary end points. After adjustment for standard risk predictors and levels of CRP and brain natriuretic peptide, MCP-1 levels greater than 238 pg/mL remained associated with mortality and with each of the composite end points. Increasing quartiles of MCP-1 plasma levels measured at 4 months were also associated with mortality and with most composite end points; however, no association was observed between 4-month MCP-1 quartiles and subsequent myocardial infarction. The results obtained from the A to Z trial suggest that MCP-1 may have value as a biomarker for risk stratification in both the initial and the chronic phases after an ACS. In contrast to CRP, MCP-1 levels may be an indicator of long-term cardiovascular risk rather than a marker of acute prognosis.

What are the mechanisms responsible for adverse prognosis in patients with ACS who have elevated MCP-1 levels?

Increased cardiovascular risk in ACS patients with elevated MCP-1 levels is not caused by increased cardiac injury because the baseline levels of MCP-1 after an acute coronary event do not appear to reflect the extent of cardiomyocyte necrosis [39]. However, the critical involvement of MCP-1 in the pathogenesis of atherosclerosis, plaque destabilization, and postinfarction remodeling suggests several distinct mechanisms that may be responsible for adverse prognosis in patients with elevated MCP-1 levels [43]. First, baseline elevation of plasma MCP-1 may reflect enhanced expression of the chemokine in atheromatous lesions, reflecting a higher burden of atherosclerotic disease. Second, enhanced systemic activation of the MCP-1 axis may exert prothrombotic effects, resulting in recurrent coronary events. Third, enhanced and prolonged elevation of plasma MCP-1 may identify patients who mount a more intense cardiac inflammatory reaction following a coronary event, or show impaired resolution and defective containment of the postinfarction inflammatory response.

Induction of proinflammatory mediators and leukocyte infiltration plays an essential role in phagocytotic removal of dead cells and matrix debris from the infarcted myocardium. However, this acute localized inflammatory response is transient and is followed by resolution of the inflammatory infiltrate and deposition of fibrous tissue [24]. A crucial commitment is made during the late stages of the inflammatory phase to convert the response from phagocytosis and clearance of dead cells and debris to a mode that promotes tissue repair and scar formation [44]. Inhibition of chemokine and cytokine synthesis after a dramatic early peak is crucial for the repair process, preventing prolonged expression of inflammatory mediators in the healing infarct, and suppressing continuous leukocyte recruitment, extensive matrix degradation, and injury. Thus, optimal healing requires mechanisms inhibiting chemokine and cytokine synthesis, resulting in resolution of the inflammatory infiltrate and transition to fibrous tissue deposition. Sustained inflammation following the acute event may result in extensive matrix degradation and adverse cardiac remodeling. The findings from the A to Z study are consistent with this hypothesis: prolonged elevation of MCP-1 levels may reflect impaired mechanisms of resolution of inflammation, leading to enhanced adverse remodeling and increased mortality,

without affecting the incidence of new myocardial infarction. Studies examining the relation between MCP-1 plasma levels and the extent of remodeling following infarction are needed to explore this concept.

Although age, cigarette smoking, triglyceride levels, and body mass index are clinical correlates of MCP-1 levels in large populations, genetic variations play a more important role in MCP-1 plasma level variability [45]. In the Framingham Heart Study Offspring cohort [45], individuals carrying the MCP-1-2578G allele had higher circulating MCP-1 levels and exhibited an increased risk of myocardial infarction. Whether MCP-1 polymorphisms are associated with enhanced serum MCP-1 levels and worse prognosis after an ACS event remains to be investigated.

Can MCP-1 levels guide pharmacotherapy?

MCP-1 may be of potential value in guiding pharmacologic treatment in patients with ACS. 3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibition decreases MCP-1 expression in atherosclerotic vessels [46] and reduces plasma MCP-1 levels in hypercholesterolemic patients [47]. It has been suggested that the beneficial effects of statins in patients with myocardial infarction may be mediated at least in part through decreased MCP-1 expression. The A to Z trial examined the hypothesis that elevated MCP-1 levels could identify patients more likely to benefit from aggressive statin treatment. However, the findings demonstrated that the effects of early intensive treatment with simvastatin are independent of baseline MCP-1 plasma levels in patients with ACS, suggesting that higher MCP-1 levels do not identify patients who derive incremental benefit from statin therapy. The modest effects of aggressive statin treatment on MCP-1 levels do not exclude a significant role of MCP-1 inhibition in mediating the beneficial actions of the statins, but may suggest that therapeutic interventions aimed at further reducing MCP-1 levels in patients with ACS may provide additional benefit. Experimental studies have demonstrated that disruption of the MCP-1 signaling pathway attenuates dilative remodeling following reperfused myocardial infarction [28], suggesting that MCP-1 may be a novel pharmacologic target in patients with acute coronary events [48]. However, a word of caution should be raised regarding the potential consequences of overly aggressive suppression of the MCP-1 axis in the infarcted myocardium, as absence of MCP-1 results in attenuated postinfarction left ventricular remodeling at the expense of impaired phagocytosis and delayed replacement of injured cardiomyocytes with granulation tissue. In patients with acute myocardial infarction, delayed phagocytosis of dead cardiomyocytes may prolong activation of inflammatory pathways, resulting in extension of injury and increased matrix degradation. The effects of MCP-1 inhibition in large mammalian models of infarction should be carefully studied before identifying MCP-1 as a potential target for therapeutic intervention.

Conclusions

MCP-1 is critically involved in formation and progression of atheromatous lesions, may contribute to destabilization of the plaque, and appears to be an essential mediator in adverse remodeling following myocardial infarction. Despite its central involvement in the pathogenesis of atherosclerotic disease, MCP-1 may not be a useful biomarker for risk prediction in patients with subclinical atherosclerosis. However, emerging evidence suggests that baseline and sustained elevation of MCP-1 plasma levels may be an independent predictor of mortality following an acute coronary event. Prolonged elevation of systemic MCP-1 levels following ACS may reflect increased atherosclerotic burden, may be associated with "vulnerable lesions," or may identify patients with impaired resolution of the post-infarction inflammatory response who are likely to exhibit accentuated adverse remodeling. Further research is required to dissect the mechanisms responsible for adverse prognosis in patients with elevated MCP-1 plasma levels and to examine whether MCP-1 is a promising therapeutic target in patients with ACS.

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Disclosures

No potential conflicts of interest relevant to this article were reported.

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