The chemokines are a family of small heparin-binding proteins with a strikingly similar tertiary structure. There are approximately 50 human chemokines, and they can be classified into CC, CXC, C, or CX3C subfamilies based on the number of amino acids between the first 2 of the 4 conserved cysteine residues that characterize chemokine structure. Monocyte chemoattractant protein (MCP)-1/CCL2, the most thoroughly characterized CC chemokine, was identified as a monocyte–specific chemoattractant that was later shown to attract T lymphocytes and natural killer cells, but not neutrophils. Enhanced expression of MCP-1 was shown in a variety of pathological conditions, associated with inflammation and mononuclear cell infiltration.

Inflammation plays a crucial role in the initiation and progression of atherosclerotic disease and may be critically involved in the pathogenesis of plaque rupture and thrombosis. In the early stages of atherosclerosis blood monocytes diapedes into the subendothelium, where they ingest lipid to become the foam cells of the fatty streak. Extensive experimental evidence suggests that MCP-1 is highly expressed in atherosclerotic plaques (1) and mediates macrophage recruitment in the atheromatous lesion. 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 (2). Thus, MCP-1 may be the molecular link between oxidized lipoproteins and foam cell recruitment into the vessel wall. Deletion of the MCP-1 gene in LDL receptor–deficient mice (3) and in animals overexpressing human apolipoprotein B (4) protected from the development of diet-induced atherosclerosis, dramatically reducing macrophage recruitment in the aortic wall, without altering lipoprotein metabolism.

The potential role of MCP-1 in the progression of atherosclerotic disease and plaque rupture is less established. Monocyte chemoattractant protein-1 induces smooth muscle cell proliferation and may exert angiogenic effects promoting neovessel formation in the plaque; these actions may lead to rapid progression of the lesion. Additionally, MCP-1 may play a role in disruption of the atherosclerotic plaque by inducing matrix metalloproteinase expression and release. Also, MCP-1 may have procoagulant properties, inducing tissue factor synthesis and activity in smooth muscle cells (5). Although direct proof of the in vivo significance of these mechanisms is lacking, an inhibitory antibody to MCP-1 and -5 administered to apolipoprotein E−/− mice induced a stable plaque phenotype with increased collagen content (6).

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 after an acute coronary event (7). Myocardial infarction triggers a local inflammatory reaction that results in formation of a scar and is closely intertwined with remodeling of the infarcted ventricle. Monocyte chemoattractant protein–1 expression is markedly but transiently induced in infarcted hearts and critically regulates the healing response. Monocyte chemoattractant protein–1 null mice show reduced macrophage infiltration, delayed phagocytosis of dead cardiomyocytes, and suppressed cytokine synthesis followed by decreased myofibroblast accumulation in the infarcted myocardium. In the absence of MCP-1, suppression of the inflammatory response and reduced fibroblast infiltration result in attenuated dilative remodeling of the infarcted ventricle (8). 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 (9). Thus, timely resolution of the inflammatory response after myocardial infarction is critical for optimal healing.

The potential involvement of MCP-1 in the pathogenesis of myocardial infarction and cardiac remodeling does not necessarily imply that plasma levels of MCP-1 can serve for risk prediction in patients with acute coronary syndromes (ACS) (10). Plasma MCP-1 levels may not reflect the activation of the MCP-1 axis in the vascular wall or the infarcted heart because of 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. In addition, pharmacological interventions may influence plasma chemokine levels in patients with ACS. Despite these theoretical concerns, clinical investigations have suggested that in patients with ACS, high baseline plasma MCP-1 levels are associated with an increased risk of death and recurrent ischemic events independent of standard risk predictors (11). These studies suggested that MCP-1 may be an attractive surrogate biomarker in patients with ACS.

In this issue of the Journal, de Lemos et al. (12) examined whether serial measurement of plasma MCP-1 levels in a large population of patients with an ACS adds prognostic value to standard risk assessment tools and established biomarkers. After adjustment for standard risk predictors and levels of C-reactive protein and B-type natriuretic peptide, high baseline MCP-1 levels remained independently associated with long-term mortality and major adverse cardiac outcomes. In addition, MCP-1 levels measured 4 months after the coronary event also provided independent prognostic information. The study extends previous investigations suggesting that MCP-1 may be valuable for risk stratification of patients in both the early and late stage after an acute coronary event. In addition, the findings raise an intriguing question regarding the potential role of MCP-1 in patients with coronary disease. Why do patients with persistently elevated MCP-1 plasma levels have adverse outcomes after an ACS event?

Several distinct mechanisms may be responsible for the adverse prognosis of patients with elevated MCP-1 levels (Fig. 1). First, baseline elevation of plasma MCP-1 may reflect enhanced expression of the chemokine in atherosclerotic lesions, resulting in increased macrophage recruitment and more extensive 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 after a coronary event, or show impaired resolution of the post-infarction inflammatory response. Sustained inflammation after the acute event may result in adverse cardiac remodeling. It should be noted that the baseline levels of MCP-1 after an acute coronary event do not seem to reflect the extent of injury. Because in the A to Z (Aggrastat to Zocor) study troponin levels were not measured in a core laboratory, quantitative evaluation of the relation between MCP-1 levels and the extent of cardiomyocyte injury was not possible. However, in the OPUS-TIMI (Orbofiban in Patients with Unstable coronary Syndromes-

Figure 1: Why Do Patients With Elevated Plasma MCP-1 Levels Have Adverse Prognosis After an ACS Event?

(A) High plasma monocyte chemoattractant protein (MCP)-1 levels may reflect increased synthesis of the chemokine by vascular cells leading to more extensive atherosclerotic disease. Monocyte chemoattractant protein-1 is immobilized on the luminal surface of the endothelium through binding with proteoglycans and mediates mononuclear cell (M) recruitment into the subendothelial space. Monocytes differentiate into macrophages (Ma) and ingest lipids to form foam cells (FCs). Monocyte chemoattractant protein-1 is involved in FC formation, one of the earliest manifestations of atherosclerosis. (B) 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 (V, neovessel). Also, MCP-1 may induce matrix metalloproteinase (MMP) synthesis, promoting matrix degradation and plaque disruption, and may up-regulate tissue factor (TF) expression exerting procoagulant effects. (C) Prolonged increase of plasma MCP-1 levels after an acute coronary syndrome event may identify patients showing an enhanced inflammatory response in the healing myocardium. The induction of MCP-1 in the infarcted myocardium during the inflammatory phase of healing mediates macrophage recruitment resulting in clearance of the infarct from dead cells and matrix debris, but also seems to play a role in the pathogenesis of adverse remodeling. Timely repression of MCP-1 synthesis is crucial for optimal healing; sustained inflammation results in adverse remodeling of the infarcted ventricle.
Thrombolysis In Myocardial Infarction) 16 study, the prognostic association of MCP-1 was independent of cardiac troponin levels (11).

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 (13). In the Framingham Heart Study offspring cohort, individuals carrying the MCP-1-2578G allele had higher circulating MCP-1 levels and showed an increased risk of myocardial infarction (13). Whether CCL2/MCP-1 polymorphisms are associated with enhanced serum MCP-1 levels and worse prognosis after an ACS event remains to be investigated.

The findings of the study may also have therapeutic implications. It has been shown that 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibition decreases MCP-1 expression in atherosclerotic vessels (14) and reduces plasma MCP-1 levels. It has been suggested that the beneficial effects of statins in patients with myocardial infarction may be mediated through decreased MCP-1 expression. Thus, elevated MCP-1 levels could identify patients more likely to benefit from aggressive statin treatment. The current study suggested that the effects of early intensive treatment with simvastatin are independent of baseline MCP-1 plasma levels. 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 aiming at further reducing MCP-1 levels in patients with ACS may provide additional benefit. Experimental studies have shown that disruption of the MCP-1 signaling pathway attenuates dilative remodeling after reperfused myocardial infarction (8), suggesting that MCP-1 may be a novel pharmacological target in patients with acute coronary events. However, a word of caution should be raised regarding the potential consequences of overly aggressive suppression of MCP-1 in the infarcted myocardium: absence of MCP-1 results in attenuated post-infarction left ventricular remodeling at the expense of impaired phagocytosis and delayed replacement of injured cardiomyocytes with granulation tissue. Delayed phagocytosis of injured cardiomyocytes may increase the arrhythmogenic potential or predispose to mechanical complications in patients with myocardial infarction. The effects of MCP-1 inhibition in large mamma-

**REFERENCES**


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