Monocyte chemoattractant protein-1 (MCP-1, also known as CCL2) is a chemokine of the C-C type which recruits circulating monocytes to sites of inflammation. Over the past several years, MCP-1 has become established as a major factor in the development of atherosclerosis through its promotion of monocyte/macrophage accumulation in atherosclerotic plaques, leading in turn to chronic inflammation, smooth muscle cell proliferation, and plaque instability. Although not present in normal blood vessels, MCP-1 protein and mRNA are strongly expressed in areas of atherosclerosis.\(^2\) Knock out of the MCP-1 gene or the receptor for MCP-1, C-C chemokine receptor (CCR)-2, are associated with a decrease in the extent of atherosclerosis in murine models.\(^3\)\(^5\)

MCP-1 is produced by endothelial cells, vascular smooth muscle cells, and macrophages in atherosclerotic plaques. Oxidized LDL in the arterial wall may upregulate the MCP-1 gene in vascular cells and stimulate the local adhesion of monocytes to endothelial cells.\(^6\) LDL-C has been shown to upregulate CCR-2 expression on monocytes, and monocyte CCR2 expression is dramatically increased in hypercholesterolemic patients compared with normal controls.\(^7\)

There has been increasing interest in the role of MCP-1 in other inflammatory conditions, including post-ischemic inflammation. A study published in this issue of Circulation Research by Dewald et al demonstrates that MCP-1 plays an important role in the healing of necrotic areas of myocardium following coronary artery occlusion and reperfusion.\(^8\) Mice with disruption of the MCP-1 gene exhibited striking delays in the recruitment of macrophages into the healing infarct and in the replacement of injured myocytes by granulation tissue without any effect on neutrophil mobilization.\(^9\) MCP-1 null mice had decreased and delayed infiltration of macrophages, decreased expression of important cytokines, such as TNF\(\alpha\), IL-1\(\beta\), TGF\(\beta\), and IL-10, decreased macrophage differentiation, and diminished myofibroblast accumulation (without a change in angiogenesis) within the healing infarct.

These observations would suggest a beneficial role for MCP-1 in promoting infarct healing. The persistence of “mummified” myocytes and delay in formation of granulation tissue in MCP-1 null mice is reminiscent of the observations made 3 decades ago following the administration of high dose steroids in acute myocardial infarction. Patients treated with steroids had an increased incidence of myocardial rupture, leading to the abandoning of this potential therapy.\(^9\)

Paradoxically, however, the study by Dewald et al found that MCP-1 null mice had less post-infarct left ventricular remodeling (less left ventricular dilatation and less impairment of left ventricular function) without a change in the size of the infarct, suggesting that MCP-1 somehow causes ventricular remodeling at the same time that it promotes infarct healing. This observation is unlikely to be a random error, since other approaches to inhibiting MCP-1, including over-expression of an N-terminal deletion mutant of the MCP-1 gene,\(^10\) or genetic deletion of the MCP-1 receptor CCR-2,\(^11\) have also resulted in less post-infarct left ventricular remodeling.

The biological pathways responsible for post-infarct ventricular remodeling are complex and not fully understood. Remodeling occurs more than several weeks following an acute myocardial infarction, and is dependent in large part on the size of the infarcted region. The larger the infarct, the more likely the infarct region is to thin and become aneuryssmal over time, and the noninfarcted region to stretch (related to myocyte elongation and myofiber rearrangement or “slippage”), and become hypertrophied and fibrotic. Clinically, these processes result in ventricular dilatation, reduced ventricular function, and often, chronic heart failure.

Early reperfusion to salvage injured but viable myocytes and reduce the size of the infarcted region is an accepted approach for preventing post-infarct ventricular remodeling. The use of angiotensin converting enzyme inhibitors to reduce LV wall stress (although other effects of these inhibitors may also be important, such as their anti-inflammatory effects) is also standard anti-remodeling therapy. Studies in animal models utilizing granulocyte colony-stimulating factor (G-CSF) have suggested that ongoing apoptosis within the infarct and peri-infarct regions may contribute to ventricular remodeling, presumably by increasing the size of the infarcted region. G-CSF has been shown to limit remodeling by inducing anti-apoptotic proteins through activation of the Jak/Stat pathway.\(^12\) Probably equally important, G-CSF also appears to limit ventricular remodeling by promoting the expression of collagen in the infarcted area, perhaps through the upregulation of the “fibrotic cytokine” transforming growth factor-\(\beta\) (TGF-\(\beta\)).\(^13\) Rats with myocardial infarction treated with G-CSF had higher expression of TGF-\(\beta\) mRNA in the infarcted area at 3 days post-infarct, along with earlier peaking and higher levels of procollagen type I and III mRNA, and more prominent collagen accumulation in the infarcted area at 7 days. Presumably, enhanced expression of collagen in the infarcted segment makes the
extracellular matrix stronger and less prone to thinning and aneurysm formation.

However, as collagen is laid down in the infarcted area, it is also being degraded by matrix metalloproteinases (MMPs), which in turn are regulated by tissue inhibitors of MMPs (TIMPs). Genetic deletion of TIMP-1 in a murine infarct model results in accelerated LV remodeling, which can be reversed by pharmacological inhibition of MMPs by PD-166793.14 MMPs therefore appear to be an important determinant of remodeling through their effect on collagen content in the infarct area.

Processes occurring in the noninfarcted area may also contribute to post-infarct remodeling. Sustained or recurrent elevations of cytokines, such as IL-1β or TNF-α in noninfarcted myocardium, away from the original site of injury, are associated with collagen deposition and interstitial fibrosis, which is associated with ventricular remodeling.15 IL-1β increases expression of MMPs-13, -2, and -9 in cultured cardiac fibroblasts, whereas TNF-α increases expression of pro-MMP-3.16 Infusion of C-type natriuretic peptide in a rat infarct model produced a significant attenuation of ventricular remodeling which was attributed to its anti-fibrotic and anti-hypertrophic effects in the noninfarcted region.17 It therefore seems that fibrosis in the infarct area may be beneficial, whereas fibrosis in the noninfarct area may be harmful in terms of ventricular remodeling.

How does all of this relate to the apparently divergent effects of MCP-1 on infarct healing and ventricular remodeling reported by Dewald et al in this issue of Circulation Research? MCP-1 has important effects on monocytes/macrophages in addition to promoting and directing chemotaxis. In vitro, MCP-1 activates the respiratory burst of monocytes and induces the expression of the pro-inflammatory cytokines IL-6 and IL-1β,18 which in turn may regulate the expression of TGF-β. MCP-1 was shown to stimulate collagen expression via endogenous upregulation of TGF-β19 and MMP expression in stimulated fibroblasts.20 Therefore, even while MCP-1 was promoting macrophage recruitment, myofibroblast differentiation, and replacement of necrotic myocytes with granulation tissue in the infarct, it may also have stimulated the expression of high levels of pro-inflammatory cytokines by these macrophages, resulting in the downstream expression of MMPs, with a net adverse effect on LV remodeling.

The challenge remaining is to translate these interesting findings on MCP-1 in murine infarct models to useful therapy in patients with acute myocardial infarction. Ventricular remodeling, with resultant chronic heart failure, is a major clinical problem for which there are currently only incomplete solutions. MCP-1 is likely to have a major role in this process, but further information is needed about how exactly MCP-1 produces adverse ventricular remodeling to devise appropriately targeted therapies. Is the adverse effect actually mediated by MMPs, and if so, by which ones, produced by and acting on which cell types, by what pathways, over what time course? As pointed out by Dewald et al,8 based on their studies, MCP-1 inhibition might appear to represent an attractive approach to limiting post-infarct remodeling, but the results must be put into proper context. “It is possible that in patients with acute myocardial infarction, delayed phagocytosis of injured cardiomyocytes may increase the arrhythmogenic potential or predispose to mechanical complications, such as rupture, or ventricular aneurysm formation.” Because murine models only rarely exhibit these complications, translational studies are needed in large mammalian models of infarction to understand the real therapeutic potential and safety of targeting MCP-1. Going after downstream targets of MCP-1, such as specific MMPs, or focusing on tissue MMP inhibitors (TIMPs), might in fact better achieve the therapeutic goals with fewer unwanted side effects.

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References


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