Chemokines on the Rise
MCP-1 and Restenosis
Ann Marie Schmidt, David M. Stern

Mechanisms underlying restenosis after percutaneous transluminal coronary angioplasty (PTCA) are important to elucidate, as evidenced by the recent success of monoclonal antibodies to platelet glycoprotein IIb/IIIa in preventing restenosis. In this issue of Arteriosclerosis, Thrombosis, and Vascular Biology, a report by Cipollone et al describes the association of monocyte chemoattractant protein-1 (JE/MCP-1) with restenosis after coronary angioplasty. As discussed below, in view of the biological properties of JE/MCP-1, increased blood levels of this chemokine are likely to represent far more than a simple marker of local vascular disease; rather, we speculate that enhanced expression of JE/MCP-1 provides a window into the pathogenesis of vascular smooth muscle cell (SMC) and mononuclear phagocyte (MP) activation, which underlies restenosis.

Chemokines are a large group of low-molecular-weight polypeptides (8 to 16 kDa) originally recognized for their ability to mediate migration of leukocyte populations toward foci of immune/inflammatory stimuli. This includes facilitation of leukocyte-endothelial interaction and cell migration itself. JE/MCP-1, the prototypical C-C chemokine, is associated with chronic vascular disorders, such as atherosclerosis, unstable angina, and congestive heart failure. As a member of the group of “immediate-early” genes whose expression occurs with a rapid time course after exposure to stimuli, the brief interval between injury to the vessel wall (ie, angioplasty) and expression of JE/MCP-1 might have been predicted. In a model of balloon injury to normal rabbit aortas, upregulation of JE/MCP-1 transcripts was noted by 1 hour and reached a maximum by 4 hours, returning to baseline by 8 hours. In view of the absence of invading MPs during these early times (1 to 4 hours) and the completeness of endothelial denudation, the authors concluded that vascular SMCs were the likely source of JE/MCP-1. These data are consistent with subsequent results in a rat carotid injury model in which early expression of JE/MCP-1 was noted, and administration of neutralizing polyclonal antibody to JE/MCP-1 with different regimens during the first 5 days was associated with diminished neointimal expansion. In a porcine iliac artery angioplasty model, early expression of JE/MCP-1 transcripts (by 2 hours) was also observed. JE/MCP-1 expression was maximal in the latter model at 8 hours and declined to baseline by 16 to 24 hours. Immunohistochemical analysis of the site of injury performed at 8 hours demonstrated JE/MCP-1 to be predominately associated with MPs. Putting together these observa-
tions, it would be predicted that induction of JE/MCP-1 transcripts occurs at the earliest stages after vascular injury in vascular SMCs, and shortly thereafter, in infiltrating MPs. The observations of Cipollone et al. suggest an important addition to this view of JE/MCP-1 and the biology of restenosis accompanying angioplasty. In a study of 50 patients undergoing PTCA, the authors observed that patients with restenosis had statistically significant elevations in plasma MCP-1 compared with nonrestenotic patients (mea apolipoprotein E–deficient (apoE−/−) mice. Previous studies showed that 1, 5, 15, and 180 days). In contrast, 2 other chemokines, regulated on activation normally T cell expression and secreted and interleukin-8, did not follow a similar pattern. There was no difference in baseline levels of JE/MCP-1 in patients who would/would not develop restenosis. Based on multivariate regression analysis, MCP-1 plasma levels at 15 days after angioplasty proved to be a significant independent predictor of restenosis. Two important caveats related to this study, in terms of extrapolation to the larger general population of patients undergoing angioplasty, concern (1) the exclusion of patients who underwent stenting after PTCA from the study and (2) the relatively small number of patients evaluated. However, despite these limitations, this work raises important issues for future study.

In contrast to the previous focus on early expression of JE/MCP-1 after angioplasty in animals with normal vascular anatomy, the data of Cipollone et al. suggest that in human arteries with underlying atherosclerosis, induction of JE/MCP-1 may be more sustained. There are several mechanisms that could underlie these observations, such as prolonged activation of nuclear factor-κB and Egr-1 in the injured vessel wall. In a role for peroxisome proliferator-activated receptor-α, platelet-derived growth factor, and/or diminished local nitric oxide production might be involved in the second phase of JE/MCP-1 expression. However, the key point is that one can surmise a positive feedback loop in which mechanisms that would ordinarily limit JE/MCP-1 to a brief pulse (coincident with expression of other chemokines) early after injury of the normal vessel wall have been supplanted by a more sustained stimulus in which JE/MCP-1 expression is potentiated (Fig. 1). Such prolonged JE/MCP-1 production could have autocrine/paracrine effects on MPs and SMCs at the site of the lesions and would be reflected in the apparent activation of MPs observed in patients with increased levels of JE/MCP-1.

Viewed in this context, the observations of Cipollone and colleagues provide a potential opportunity to translate results from animal models and clinical observations to therapeutic concepts. At the very least, plasma levels of JE/MCP-1 provide a valuable index of MP activation after angioplasty and are likely to be reflective of events occurring locally in the injured vessel wall. If this extrapolation proves to be valid at the level of pathogenesis of vascular lesions, then interception of the interaction of JE/MCP-1 with its receptor could provide a future therapeutic modality for patients at risk for restenosis.

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