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.1,2 In this issue of *Arteriosclerosis, Thrombosis, and Vascular Biology*, a report by Cipollone et al3 describes the association of monocyte chemotactic 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.4,5 This includes facilitation of leukocyte-endothelial interaction and cell migration itself.6 JE/MCP-1, the prototypical C-C chemokine, is associated with chronic vascular disorders, such as atherosclerosis,7–12 unstable angina,13 and congestive heart failure,14 as well as inflammatory states.4,5,15–19 This chemokine exerts its biological properties of JE/MCP-1, increased blood levels of this chemokine appear to be toward MPs. Activation of MPs mediated by JE/MCP-1 involves at least 2 phases: a short-term phase, including elevation of cytosolic calcium, actin polymerization, and upregulation of β2-integrins, thus allowing cell migration and tight binding to endothelial counterreceptors,4,5 and a longer-term phase, involving expression of the procoagulant initiator tissue factor26,27 and intercellular adhesion molecule-1 (the latter 2 occur in SMCs and MPs) (and other inflammation-associated genes), as well as generation of reactive oxygen intermediates.25,28,29 Taken together, these events form an important shift in cellular properties toward an activated state, and their relevance to host response mechanisms is emphasized by the association of JE/MCP-1 expression with recruitment of MPs into tissues. The latter conclusion is supported by results of studies in transgenic models with targeted expression of JE/MCP-1 expression30–32 and experiments in JE/MCP-1–deficient mice,33 as well as correlative work (see Reference 8) and studies with blocking antibodies.34

In the context of atherosclerotic vascular disease, there is compelling evidence for a pathogenic role of JE/MCP-1. Expression of JE/MCP-1 has been noted in cell types critical to the formation of such vascular lesions, including endothelium, MPs, and smooth muscle. Experiments with mice rendered genetically deficient in JE/MCP-1 or its key target receptor, CCR2, have shown diminished formation of atherosclerotic lesions.11,35 Bone marrow transplantation with cells from mice overexpressing a JE/MCP-1 transgene into apolipoprotein E–null animals resulted in repopulation of the bone marrow with cells bearing the transgene, along with increased lesion formation, oxidized lipids, and macrophage infiltration.9 The observed elevation of JE/MCP-1 in patients with acute myocardial infarction13 draws this chemokine into the biology of acute events associated with plaque rupture and vascular wall remodelling. These observations are consistent with the results of studies in a canine model of myocardial ischemia/reperfusion, in which JE/MCP-1 expression was noted within an hour of the ischemic insult.36

As a member of the group of “immediate-early” genes whose expression occurs with a rapid time course after exposure to stimuli,37 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.38 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.39 In a porcine iliac artery angioplasty model, early expression of JE/MCP-1 transcripts (by 2 hours) was also observed.40 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-
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-1.3

Viewed in this context, the observations of Cipollone and colleagues1 suggest 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.

References
5. Wada K, Yokohama H, Furuichi K, Kobayashi K-I, Harada K, Naruto M, Minamino N, Kishida Y, Akutsu T, Terai M, Fujii E, Shimizu T, Sano H. Circulating JE/MCP-1 in patients who would/would not develop restenosis 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 vasculature, the data of Cipollone et al3 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.41–44 In addition, a role for peroxisome proliferator-activated receptor-α,45 platelet-derived growth factor,38,46 and/or diminished local nitric oxide production37,46 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

In contrast to the previous focus on early expression of JE/MCP-1 after angioplasty in animals with normal vasculature, the data of Cipollone et al3 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.41–44 In addition, a role for peroxisome proliferator-activated receptor-α,45 platelet-derived growth factor,38,46 and/or diminished local nitric oxide production37,46 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
27. Ernofsson M, Siegbahn A. PDGF-BB and MCP-1 induce peripheral  
28. Maghazachi A, al-Aoukaty A, Schall T. C-C chemokines induce the  
expression of MCP-1 in human aortic smooth muscle and THP-1 cells.  
29. Rollins B, Morrison E, Stiles C. Cloning and expression of JE, a gene  
inducible by PDGF and whose product has cytokine-like properties.  
30. Kolattukudy P, Quach T, Bergese S, Breckenridge S, Hensley J,  
Altschuld R, Gordillo G, Klenotic S, Orosz C, Parker-Thornburg J.  
Myocarditis induced by targeted expression of the MCP-1 gene in murine  
R, Lira S. Controlled recruitment of monocytes and macrophages to  
Transgenic MCP-1 in pancreatic islets produces monocyte-rich insulin  
secreting islets without diabetes: abrogation by a second transgene expressing  
33. Rollins B. MCP-1: a potential regulator of monocyte recruitment in  
MCP-1/JE in monocyte/macrophage-dependent IgA immune complex  
35. Taubman M, Rollins B, Poon M, Marmur J, Green R, Berk B, Nadal-  
Ginard B. JE mRNA accumulates rapidly in aortic injury and in PDGF-  
D. Egr-1, a master switch coordinating upregulation of divergent gene  
37. Santiago F, Lowe H, Kavurma M, Chesterman C, Baker A, Atkins D,  
Khachigian L. New DNA enzyme targeting Egr-1 mRNA inhibits  
Hama S, Borromeo C, Evans R, Berliner J, Nagy L. Role for PPAR-γ  
in oxidized phospholipid-induced synthesis of monocyte chemotactic  
protein-1 and interleukin-8 by endothelial cells. Circ Res. 2000;87:  
516–521.  
39. Bogdanov V, Poon M, Taubman M. PDGF-specific regulation of the JE  
24932–24938.  
Myocarditis induced by targeted expression of the MCP-1 gene in murine  
41. Fuentes M, Durham S, Swerdel M, Lewin A, Bartos D, Megill J, Bravo  
R, Lira S. Controlled recruitment of monocytes and macrophages to  
42. Grewal I, Rutledge B, Fiorillo J, Gu L, Gladue R, Flavell R, Rollins B.  
Transgenic MCP-1 in pancreatic islets produces monocyte-rich insulin  
secreting islets without diabetes: abrogation by a second transgene expressing  
43. Rollins B. MCP-1: a potential regulator of monocyte recruitment in  
D. Egr-1, a master switch coordinating upregulation of divergent gene  
Hama S, Borromeo C, Evans R, Berliner J, Nagy L. Role for PPAR-γ  
in oxidized phospholipid-induced synthesis of monocyte chemotactic  
protein-1 and interleukin-8 by endothelial cells. Circ Res. 2000;87:  
516–521.  
46. Bogdanov V, Poon M, Taubman M. PDGF-specific regulation of the JE  
24932–24938.  
H, Takeya M, Yoshimura T, Takeshita A. Inhibition of NO synthesis  
induces inflammatory changes in MCP-1 expression in rat hearts and  
Chemokines on the Rise: MCP-1 and Restenosis
Ann Marie Schmidt and David M. Stern

doi: 10.1161/01.ATV.21.3.297

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/21/3/297