MCP-1 Induces a Novel Transcription Factor With Proapoptotic Activity

Kiril Bidzhekov, Alma Zernecke, Christian Weber

Over the past years, the crucial and versatile functions of the prototypic CC chemokine monocyte chemotactic protein-1 (MCP-1/CCL2) and its cognate receptor CCR2 in the recruitment of monocytes/macrophages during atherogenesis and other inflammatory processes in the cardiovascular system have been well established. Although MCP-1 is not expressed in healthy vessels, various stimuli (e.g., tumor necrosis factor [TNF] and other cytokines) can induce the expression and secretion of MCP-1 in endothelial cells, vascular smooth muscle cells (SMCs), or cardiomyocytes, which by triggering and sustaining leukocyte accumulation may in turn promote chronic inflammation.

Elevated levels of circulating MCP-1 have been found in patients with congestive heart failure and coronary artery disease and have been adversely correlated with disease progression. In acute coronary syndromes, MCP-1 plasma levels have been associated with long-term clinical outcomes. Moreover, the blockade of MCP-1/CCR2 functions has been shown to ameliorate heart failure, cardiac remodeling after myocardial infarction, autoimmune myocarditis, but also vascular remodelling and neointimal hyperplasia induced by mechanical or hypertensive injury, corroborating the importance of the MCP-1/CCR2 axis in cardiovascular pathology. Although a substantial body of evidence has now been gathered on MCP-1/CCR2 functions on leukocytes and signal transduction pathways, molecular insights into the cellular gene expression responses triggered by MCP-1 binding to CCR2 remain limited.

In this issue of *Circulation Research*, Zhou et al report the identification of a novel protein, designated MCPIP (MCP-induced protein), which is expressed in human monocytes and cardiomyocytes after stimulation with MCP-1. Characterization of its gene structure and position in the human and mouse genome, further cloning and protein analysis of MCPIP revealed two proline-rich regions, a nuclear localization signal sequence and a zinc finger motif characteristic of a DNA binding transcription factor. Luciferase reporter gene assays and mutational analysis confirmed MCPIP to function as a transcriptional activator localized in the nucleus, whereas TUNEL assays and microarray analysis further unveiled that MCPIP upregulates members of the apoptotic gene family involved in the induction of cell death. Collectively, these results provide a novel molecular pathway, by which MCP-1/CCR2 signal transduction is linked to transcriptional gene regulation leading to apoptosis.

Because MCP-1 and cell death have both been implicated in the development of cardiovascular disease, the authors further explored the role of MCPIP in ischemic heart disease in a transgenic mouse model of cardiomyocyte-targeted expression of MCP-1. In correlation with the appearance of symptoms of heart failure, nuclear degradation, and vacuolation at around 6 months of age, transcripts of MCPIP were identified in cardiomyocyte nuclei and were found to increase with the progression of ventricular dysfunction and age of the animals. Notably, prolonged exposure to MCP-1 in this model induced CCR2 expression in cardiomyocytes beginning at 4 months of age, sustaining and possibly reinforcing the impact of MCP-1/CCR2 on MCPIP and the induction of apoptosis. Additional in vivo relevance was obtained by examining hearts explanted from ischemic and nonischemic patients, confirming a profound increase of MCPIP compared with nonischemic heart disease. Although further studies into the factors and signaling elements involved in controlling the transcription of MCPIP and its DNA binding sites, as well as coactivators and binding partners, are warranted, these findings are intriguing and shed new light on previous observations (see the Figure).

The findings obtained by Zhou et al may pertain to patients with congestive heart failure who display significantly elevated levels of MCP-1 in an inverse correlation with left ventricular ejection fraction. Moreover, the Framingham Heart Study identified a genetic polymorphism in the MCP-1 gene associated with increased MCP-1 levels and a higher prevalence of myocardial infarction. Several animal models of myocardial infarction and reperfusion injury have demonstrated an increase in MCP-1 expression, whereas genetic deficiency or gene therapy attenuates ventricular remodelling and failure. Beyond MCP-1–mediated mononuclear cell infiltration, the study by Zhou et al implies a novel and deleterious mechanism, by which MCP-1 aggravates cardiovascular disease through the induction of apoptosis in cardiomyocytes and monocytes, and which in turn may contribute to the progression of inflammation. In addition, the expression of CCR2 and the injury-related induction of MCP-1 has been described in endothelial cells. Hence, an induction of cardiomyocyte or endothelial cell apoptosis attributable to increased MCP-1 expression may account for myocardial micro-scarring in congestive or coronary heart disease or in viral or autoimmune myocarditis.
The proapoptotic transcriptional pathways elicited by MCP-1 may not only be detrimental in myocardial disease, but may also directly inflict vascular damage in the context of the frequently underlying vascular disease. In human atherosclerotic lesions, MCP-1 has been primarily detected in medial or neointimal SMCs and in monocytes/macrophages, and the genetic deletion of MCP-1 or CCR2, or anti–MCP-1 gene therapy, have been shown to protect against atherosclerotic lesion development in animal models with dietary-induced hyperlipidemia. Similarly, more complex models of neointimal hyperplasia after arterial injury revealed an increase in plasma MCP-1 levels in serum after injury and attenuated plaque formation and angiotensin II–induced remodelling in CCR2-deficient mice. Of note, MCP-1 levels are increased in patients with unstable angina and are associated with the risk for atherosclerosis, death, and myocardial infarction. On the other hand, a direct link between apoptosis of vascular SMCs and macrophages in vulnerable lesions and plaque rupture has been widely recognized. This may give rise to a model in which MCP-1 expression in atherosclerotic plaques may cause apoptosis and may thereby trigger plaque destabilization. Conversely, the massive induction of apoptosis after arterial injury is not only accompanied by a retention of MCP-1 on surface-adherent platelets but also triggers the upregulation of stromal cell-derived factor-1α and subsequent homing of vascular progenitor cells, which may constitute a compensatory mechanism for vascular repair. Of note, other chemokine/receptor pairs may serve to provide a regulatory balance for the control of apoptosis within inflammatory foci. In this regard, CCL5/CCR5 interactions have been shown to limit apoptosis in macrophages in the course of viral infections by triggering antiapoptotic signaling pathways, and may counteract proapoptotic effects of MCP-1 depending on the context or stage of vascular or myocardial disease. Put into this perspective, the findings by Zhou et al add a previously unappreciated dimension to the deleterious function of MCP-1 as a chemokine with paramount importance for the regulation of apoptotic processes during atherogenesis. Expression of MCPIP within atherosclerotic lesions and its specific functions will help to further characterize functional contributions of this new and crucial factor in cardiovascular disease.

Acknowledgments

Our research is supported by Deutsche Forschungsgemeinschaft (DFG grants WE1913/5-3 and WE1913/7-1) and Interdisciplinary Center for Clinical Research BIOMAT.

References


Key Words: chemokines ■ apoptosis ■ transcription factors ■ ischemic heart disease
MCP-1 Induces a Novel Transcription Factor With Proapoptotic Activity
Kiril Bidzhekov, Alma Zernecke and Christian Weber

Circ Res. 2006;98:1107-1109
doi: 10.1161/01.RES.0000223483.12225.80

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2006 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/98/9/1107

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org/subscriptions/