Targeting the Chemokines in Myocardial Inflammation

Nikolaos G. Frangogiannis, MD; Mark L. Entman, MD

The chemokines comprise a large family of small, highly basic proteins that play a critical role in basal and inflammatory leukocyte locomotion and trafficking.1-2 In addition to effects on cell locomotion, certain chemokines are capable of eliciting a variety of other responses affecting leukocyte adherence, activation, and degranulation, mitogenesis, and apoptosis. Furthermore, chemokines have a wide range of effects on many different cell types beyond the immune system, including endothelial cells, fibroblasts, smooth muscle cells, neurons, and epithelial cells.

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Involvement of chemokines in the pathobiology of conditions such as multiple sclerosis, HIV disease, asthma, rheumatoid arthritis, atherosclerosis, and neoplasia has been inferred by animal model experiments and supported by correlative data in humans. Although recent investigations indicated marked chemokine upregulation in the myocardial inflammatory processes associated with infarction,3-5 ischemic cardiomyopathy,6,7 allograft rejection,8,9 and myocarditis, the exact role of chemokine signaling in myocardial pathobiology remains poorly understood.

Chemokine induction seems to be a prominent response to myocardial injury in a variety of situations. In myocardial infarcts, cellular necrosis may trigger several chemokine-inducing pathways regulated through free radical generation, nuclear factor-κB activation, tumor necrosis factor-α release, and complement activation. Both CC (CCL2/monocyte chemoattractant protein-1, CCL3/macrophage inflammatory protein [MIP]-1α, and CCL4/MIP-1β) and CXC chemokines (such as CXCL10/interferon-γ inducible protein-10 and CXCL8/interleukin-8) are markedly induced in the infarcted myocardium.3,4 In contrast, brief sublethal myocardial ischemia is not associated with infarction and induces chemokine upregulation mainly through reactive oxygen intermediates.10 In the ischemic myocardium, chemokine responses are robust but transient, as the expression of inhibitory mediators suppresses chemokine synthesis leading to resolution of the inflammatory response, transition to fibrous tissue deposition, and formation of a scar.

In contrast to the well-orchestrated and transient chemokine response found in healing infarcts, acute Trypanosoma cruzi myocarditis induces persistent upregulation of chemokines associated with lymphocyte and macrophage infiltration.11,12 Although the inflammatory response in acute T cruzi infection may be essential for containment of parasite dissemination, many patients develop a persistent immune response resulting in chronic cardiomyopathy associated with extensive fibrotic changes and dysfunction. Chagas’ disease remains the major cause of cardiac pathology in Latin America. Identifying specific targets responsible for inflammatory injury without interfering with parasitic clearance is necessary to design effective therapies that inhibit cardiac fibrosis in patients with T cruzi cardiomyopathy.

In this issue of Circulation, Marino and co-workers13 describe the effects of methiolynated RANTES (Met-RANTES), a powerful CC chemokine antagonist14 (inhibiting signaling through the CCR1 and CCR5 receptors), on myocardial inflammation and injury in a mouse model of T cruzi infection. Met-RANTES treatment decreased myocardial inflammation with inflammatory leukocytes, reduced fibronectin deposition, and improved survival without interfering with parasitism. The study has obvious implications for the pathogenesis and treatment of Chagas’ disease: Chemokine inhibition may be a reasonable approach for suppressing inflammation and preventing fibrosis in patients with T cruzi infection. More importantly, this investigation offers us the opportunity to dissect the role of the chemokine response in myocardial inflammation.

Chemokine Expression in Myocardial Inflammation: Is It a Maladaptive Response?

Expression of inducible chemokines is thought to be a vertebrate cellular “SOS response” that recruits leukocytes in the area of injury.1 Although certain chemokines expressed in T cruzi-infected hearts may be important for parasitic containment, their expression may extend injury through several mechanisms.

1. The levels of their expression may be disproportionate to the extent of the initial injury.
2. Leukocyte-mediated injury may cause further induction of chemokines, resulting in persistent synthesis of chemokines and more extensive myocardial inflammation.
3. Most cell types produce numerous chemokines in response to a particular stimulus (polyserositis). Some of the induced chemokines may be “inappropriate” for a certain pathological microenvironment and may extend inflammatory injury.
4. Inflammatory responses trigger expression of inhibitory mediators to suppress the proinflammatory signals. This is particularly relevant in wound healing, where mediators such as transforming growth factor-β may downregulate
chemokine expression, leading to resolution of the inflammatory infiltrate and serving as a “switch” from inflammation to fibrous tissue deposition. Although in a healing wound, formation of a scar may be necessary for maintaining the integrity of the tissue, in diffuse inflammatory processes, transforming growth factor-β may foster development of extensive fibrosis as well as mediate suppression of inflammation. There, a maladaptive functional consequence may ensue during the repair process.

The findings of the study suggest that induction of the chemokines CCL5/RANTES and CCL3/MIP-1α in T cruzi cardiomyopathy has the characteristics of a maladaptive immune response. Persistent expression of the chemokines results in prolonged inflammatory injury and their inhibition results in improved survival, decreased inflammatory activity, and fibrosis, without affecting parasite containment. The role of other chemokines (such as CXCL10/inducible protein-10 and CXCL9/monokine induced by interferon-γ) in this pathological process may be quite different. It will be important to identify which chemokines are essential for parasite control in the infected host to design effective pharmacological interventions.

The concepts proposed above extend beyond the pathobiology of T cruzi infection. Viral myocarditis has been associated with chemokine upregulation, and MIP-1α mutant mice were resistant to Coxscackie virus-induced myocardial injury. The role of specific chemokines in injury, healing, and cardiac repair in myocardial infarction and cardiomyopathy is an area of active research in our laboratories. The explosion in the development of chemokine antagonists will undoubtedly provide us with the tools to inhibit specific chemokines. Our goal should be to identify targets for safe and effective therapeutic interventions.

Acknowledgments
This work was supported by National Institutes of Health grant HL-42550, a grant from the American Heart Association, Texas affiliate, the DeBakey Heart Center, and the Curtis Hankamer Research Fund.

References
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Circulation. 2004;110:1341-1342
doi: 10.1161/01.CIR.0000141560.18364.63
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
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