Chemokines in Myocardial Ischemia

Nikolaos G. Frangogiannis* and Mark L. Entman

Chemokine expression is markedly upregulated in healing myocardial infarcts and may play an important role in regulating leukocyte infiltration and activity and in modulating infarct angiogenesis as well as fibrous tissue deposition. The CC chemokine monocyte chemoattractant protein-1/CCL2 has important effects in infarct healing. Monocyte chemoattractant protein-1 −/− mice exhibit reduced macrophage infiltration and activation, suppressed cytokine synthesis, delayed phagocytotic removal of dead cardiomyocytes, diminished myofibroblast accumulation, and decreased ventricular remodeling after myocardial infarction. Monocyte chemoattractant protein-1 may also play an important role in the development of interstitial fibrosis in ischemic noninfarctive cardiomyopathy. CXC chemokines are also induced in healing infarcts. Interleukin-8/CXCL8 may mediate neutrophil recruitment and activation and may promote neovessel formation, whereas induction of the angiostatic and antifibrotic chemokine interferon-γ-inducible protein-10/CXCL10 may serve to prevent premature wound angiogenesis and fibrous tissue deposition in the infarct, until the injured myocardium has been cleared from dead cells and debris and a fibrin-rich provisional matrix is formed. Understanding of the role of chemokines in myocardial ischemia may result in novel strategies in the treatment of patients with ischemic heart disease.
(Trends Cardiovasc Med 2005;15:163–169)

The chemokines (Charo and Taubman 2004, Frangogiannis 2004b, Olson and Ley 2002, Rollins 1997) constitute a large family of small highly basic proteins with molecular weights in the range of 8 to 14 kDa and a strikingly similar tertiary structure (Clark-Lewis et al. 1995). Most chemokines contain four conserved cysteines that form two disulfide bonds, which confer on the chemokines their characteristic three-dimensional folding (Baggiolini 2001). Chemokines are subdivided into two main subfamilies, according to the position of the first two cysteines, which are separated by one amino acid (CXC chemokines) (Table 1) or are adjacent (CC chemokines) (Table 2). Lymphotactin (XCL1) is the only known chemokine containing only two cysteines corresponding to the second and fourth cysteines of other classes and fractalkine has three amino acids between the first two cysteines (CX3C chemokine). CXC chemokines are further classified according to the presence of the tripeptide motif glutamic acid–leucine–arginine (ELR) in the aminoterminal region. Chemokines bind to heptahelical G-protein-coupled receptors. Most receptors recognize more than one chemokine, and certain chemokines may bind to several receptors.

Chemokines play a critical role in basal and inflammatory leukocyte locomotion and trafficking (Gerard and Rollins 2001, Moser and Loetscher 2001) and their principal targets are bone-marrow-derived cells. In addition to effects on cell locomotion, certain chemokines are capable of eliciting a variety of other responses affecting leukocyte adhesion (Gerszten et al. 1999), activation and gene expression, mitogenesis, and apoptosis. It has been recently recognized that chemokines have a wide range of effects on many different cell types beyond the immune system, including endothelial cells (resulting in angiogenic or angiostatic effects) (Strieter et al. 1995a), smooth muscle cells, fibroblasts, neurons, and epithelial cells.

From the functional standpoint, chemokines can be divided broadly into two categories: homeostatic chemokines are constitutively expressed in certain tissues and may be responsible for basal leukocyte trafficking and formation of the fundamental architecture of lymphoid organs, and inducible chemokines, which are strongly upregulated by inflammatory or immune stimuli, actively participate in the inflammatory reactions by inducing leukocyte recruitment (Gerard and Rollins 2001). Although simplistic and inaccurate in its details, this concept provides insight into the role of chemokines in pathology. A wide variety of stimuli, elicited by tissue injury, can upregulate inducible chemokines, leading to a rapid marked increase in their local concentration followed by leukocyte infiltration and an inflammatory response.

• Expression and Role of Chemokines in the Infarcted Myocardium

Chemokine upregulation is a prominent feature of the postinfarction inflammatory response in several mammalian species (Frangogiannis 2004a, Frangogiannis et al. 2002c). The CXC chemokines CXCL8/interleukin (IL)-8 and CXCL10/interferon-γ-inducible protein

Abbreviations: GRO-α, Growth-Regulated Oncogene-α; IL-1β, Interleukin-1β; IL-8, Interleukin-8; IL-10, Interleukin-10; IP-10, Interferon-γ-Inducible Protein-10; MCP-1, Monocyte Chemoattractant Protein-1; MIG, Monokine Induced by γ-Interferon; MIP-1α, -β, Macrophage Inflammatory Protein-1α, -β; NF-κB, Nuclear Factor-κB; PF4, Platelet Factor 4; SDF-1, Stromal-Cell-Derived Factor-1; TGF-β, Transforming Growth Factor-β; TNF-α, Tumor Necrosis Factor-α.

Nikolaos G. Frangogiannis and Mark L. Entman are at the Section of Cardiovascular Sciences, The Methodist Hospital and the De Bakey Heart Center, Baylor College of Medicine, Houston, TX 77030, USA.

* Address correspondence to: Nikolaos Frangogiannis, MD, Section of Cardiovascular Sciences, One Baylor Plaza M/S F-602, Baylor College of Medicine, Houston, TX 77030, USA. Tel.: (+1) 713-798-4188; fax: (+1) 713-796-0015; e-mail: ngf@bcm.tmc.edu.

1050-1738/05/$-see front matter

Table 1. Properties of the CXC, C, and CX3C chemokines

Systematic name	Human common name	Mouse common name	Expression	Receptors bound
CXC chemokine family				
CXCL1	GROα	GRO/MIP-2/KC?	Inducible	CXCR2>CXCR1
CXCL2	GROβ	GRO/MIP-2/KC?	Inducible	CXCR2
CXCL3	GROγ	GRO/MIP-2/KC?	Inducible	CXCR2
CXCL4	PF4	PF4	Inducible	Unknown
CXCL5	ENA-78	GCP-2/LIX?	Inducible	CXCR2
CXCL6	GCP-2	GCP-2/LIX?	Inducible	CXCR1, CXCR2
CXCL7	NAP-2	Unknown	Inducible	CXCR2
CXCL8	IL-8	Unknown	Inducible	CXCR1, CXCR2
CXCL9	MIG	MIG	Inducible	CXCR3
CXCL10	IP-10	IP-10/CRG-2	Inducible	CXCR3
CXCL11	I-TAC	I-TAC	Inducible	CXCR3
CXCL12	SDF-1α/β	SDF-1/PBSF	Both	CXCR4
CXCL13	BCA-1	BLC	Constitutive	CXCR5
CXCL14	BRAK/bolekine	BRAK		Unknown
(CXCL15)	Unknown	Lungkine		Unknown
CXCL16	CXCL16	CXCL16		CXCR6
C chemokines				
XCL1	Lymphotactin/ATAC/SCM-1α	Lymphotactin		XCR1
XCL2	SCM-1β	Unknown		XCR1
CX3C chemokine				
CX3CL1	Fractalkine	Neurotactin/ABCD-3	Both	CX3CR1

(IP)-10 and the CC chemokine CCL2/monocyte chemoattractant protein (MCP)-1 are consistently upregulated in various models of experimental myocardial infarction (Frangogiannis et al. 2001, 2002c, Kukielka et al. 1995, Kumar et al. 1997) and may play an important role in regulating leukocyte trafficking and wound angiogenesis and repair. The mechanisms responsible for chemokine upregulation in the ischemic heart have not been elucidated; however, the factors implicated in initiating the inflammatory response (e.g., free radical generation, NF-κB activation, tumor necrosis factor-α [TNF-α] release, and complement activation) (Frangogiannis et al. 2002c) are likely to stimulate, directly or indirectly, chemokine synthesis in the injured myocardium. Evidence suggests that chemokine induction in models of brief myocardial ischemia is mediated mainly by reactive oxygen intermediates (Nossuli et al. 2001, Lakshminarayanan et al. 2001). However, in myocardial infarcts, cellular necrosis may trigger additional chemokine-inducing pathways and the relative contribution of free radical generation remains unclear. Tumor necrosis factor-α $-/-$ mice undergoing experimental infarction protocols exhibit decreased chemokine and adhesion molecule expression, suggesting an important role for TNF-α in mediating the postinfarction chemokine response (Maekawa et al. 2002).

• The Role of the CXC Chemokines

Interleukin-8 and the ELR-Positive CXC Chemokines

Interleukin-8 upregulation has been documented in canine (Kukielka et al. 1995) and rabbit (Ivey et al. 1995) models of experimental myocardial infarction. In a canine model, IL-8 synthesis was accentuated by reperfusion and was localized to the inflammatory infiltrate of the infarct border zone, as well as in small veins in the same area (Kukielka et al. 1995). Recombinant canine IL-8 markedly increased adhesion of neutrophils to isolated canine cardiac myocytes (Kukielka et al. 1995), suggesting a potential role in neutrophil-mediated myocardial injury. The exact role of IL-8 in myocardial infarction remains unclear: a recent study suggested that IL-8 neutralization significantly reduces the degree of necrosis in a rabbit model of myocardial ischemia–reperfusion without affecting neutrophil infiltration (Boyle et al. 1998). Unfortunately, elucidating the role of IL-8 in myocardial infarcts with the use of knockout and transgenic animals is hampered by the absence of an IL-8 homologue in the mouse.

Much less is known about the potential expression and role of other ELR-containing CXC chemokines in myocardial infarcts. GRO-α/KC, a potent neutrophil chemoattractant, is induced in a rat model of experimental myocardial infarction (Chandrasekar et al. 2001); however, its role in regulating the postinfarction inflammatory response remains unknown. ELR-containing CXC chemokines may have effects beyond neutrophil chemotaxis and may regulate healing by inducing angiogenesis in the infarcted heart. Deficiency of CXCR2, the main receptor for the ELR-containing CXC chemokines, resulted in significantly decreased inflammatory leukocyte recruitment in murine infarcts, suggesting a crucial role for these chemokines in inflammatory cell infiltration (Tarzami et al. 2003). However, experiments using a Langendorff preparation indicated protective effects of CXCR2 signaling on myocardial viability (Tarzami et al. 2003). The molecular basis