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REVIEW ARTICLE

Chemokines in Myocardial Infarction

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Abstract

In the infarcted myocardium, cardiomyocyte necrosis triggers an intense inflammatory reaction that not only is critical for cardiac repair, but also contributes to adverse remodeling and to the pathogenesis of heart failure. Both CC and CXC chemokines are markedly induced in the infarcted heart, bind to endothelial glycosaminoglycans, and regulate leukocyte trafficking and function. ELR+ CXC chemokines (such as CXCL8) control neutrophil infiltration, whereas CC chemokines (such as CCL2) mediate recruitment of mononuclear cells. Moreover, some members of the chemokine family (such as CXCL10 and CXCL12) may mediate leukocyte-independent actions, directly modulating fibroblast and vascular cell function. This review manuscript discusses our understanding of the role of the chemokines in regulation of injury, repair, and remodeling following myocardial infarction. Although several chemokines may be promising therapeutic targets in patients with myocardial infarction, clinical implementation of chemokine-based therapeutics is hampered by the broad effects of the chemokines in both injury and repair.

Keywords Chemokine · Leukocyte · Myocardial infarction · Cardiac remodeling · CCL2 · CXCL12

Introduction

Myocardial infarction (MI) is a leading cause of morbidity and mortality worldwide [1]. Sudden occlusion of a coronary artery results in complete loss of perfusion in the myocardial segments subserved by the vessel. Severe and sustained ischemia triggers a wavefront of cardiomyocyte death [2], leading to loss of large amounts of cardiac muscle. Because the adult mammalian heart has negligible regenerative capacity, repair of the infarcted heart is dependent on inflammation-driven formation of a scar.

Over the last 40 years, new pharmacologic therapies [3, 4] and the successful implementation of early reperfusion [5] have significantly reduced mortality in patients presenting with acute MI. However, improved survival resulted in an expanding pool of MI patients who survive the acute event, but remain at a high risk for development of chronic heart failure. The pathobiology of post-infarction heart failure is linked with "cardiac remodeling," a complex process that involves both infarcted and non-infarcted myocardial segments and results in progressive functional deterioration and an increased incidence of arrhythmias, typically associated with chamber dilation. The severity of post-infarction remodeling is dependent not only on the size of the infarct, but also on the qualitative characteristics of the reparative response [6]. Thus, following infarction, the cellular responses involved in repair may also contribute to adverse remodeling of the heart.

Inflammation is a key driver of repair and remodeling of the infarcted heart. Chemokines, a family of chemotactic cytokines with critical roles in leukocyte trafficking, are crucial mediators of inflammation in injury and repair. Over the last 20 years, a growing body of evidence has suggested that sequential mobilization of immune cell subpopulations in the infarcted heart is orchestrated by the chemokines and may play an important role in cardiac repair and remodeling [7, 8]. This review manuscript discusses our current understanding of the role of the chemokines in the infarcted heart.

The chemokine Family

Chemokines are small (8–12 kDa) chemotactic cytokines that regulate cell migration and positioning in development,

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homeostasis, and inflammatory injury [9]. In mammals, the chemokine family consists of more than 50 ligands that can be classified into 4 groups based on the positioning of their initial cysteine residues: XC, CC, CXC, and CX3C chemokine ligands. Thus, the CC chemokine ligands (CCLs) have two cysteine residues adjacent to each other, whereas the CXC-chemokine subfamily (CXCLs) has two cysteine residues separated by an amino acid [10]. The CX3C chemokine group has three amino acids between two cysteine residues and the XC chemokine group has only one N-terminal cysteine residue. Of the four chemokine groups, CCLs (28 members) are the largest subfamily, followed by the CXC-chemokines (17 members), whereas the CX3C and XC chemokine classes only have 1 and 2 members, respectively. Two subgroups of CXCLs have been identified based on the presence of the glutamic acid-leucine-arginine (ELR) motif in the aminoterminal region: the ELR+ and ELR− CXC chemokines [10]. This structural classification has important functional implications. Most CC chemokines are strong mononuclear cell chemoattractants, whereas ELR+ CXC chemokines have been implicated in neutrophil recruitment [11].

From a functional perspective, many members of the chemokine family can be categorized into inflammatory or homeostatic subgroups. The homeostatic chemokines are constitutively expressed in certain tissues and may be implicated in basal leukocyte trafficking and in formation of lymphoid organs. Inflammatory chemokines, on the other hand, are markedly upregulated in injured tissues and are key mediators in inflammatory reactions, controlling leukocyte recruitment and activation [12, 13]. This classification is crude and may represent an oversimplification, as several members of the chemokine family are expressed in normal tissues and play a role in homeostasis, but may also be induced following injury regulating inflammatory cell infiltration. However, the differences between inflammatory and homeostatic chemokines have an evolutionary origin. In mammals, inflammatory chemokines evolved rapidly, presumably in response to strong selective pressures when each species faced a new pathogen [14, 15]. For this reason, the profile and functional properties of inflammatory chemokines exhibit species-specific differences. In contrast, homeostatic chemokines are relatively ancient in evolutionary terms, and their functions are well conserved between species.

In sites of injury, inducible inflammatory chemokines are bound to glycosaminoglycans on the endothelial surface and on the extracellular matrix, and are presented to circulating or trafficking leukocytes, thus interacting with the corresponding chemokine receptors on the leukocyte surface [16, 17]. Chemokine receptors are G protein-coupled and signal via pertussis toxin-sensitive Gi-type G proteins. Most receptors recognize more than one chemokine, and certain chemokines may bind to several receptors. Despite their promiscuity, chemokine receptors only bind chemokines within the same group: CCR chemokine receptors bind to CCL chemokines, whereas CXCR receptors bind CXCL chemokines. Some studies have suggested that certain non-chemokine ligands, such as extracellular matrix degradation peptides [18], and the cytokine macrophage migration inhibitory factor (MIF) [19] can also signal through chemokine receptor binding [20–22].

The Phases of Cardiac Repair

Following myocardial infarction, severe and prolonged loss of perfusion in the myocardium subserved by the occluded vessel results in massive necrosis of cardiomyocytes. Because the adult mammalian heart has negligible regenerative capacity, repair of the infarcted myocardium is dependent on formation of a collagen-based scar. The reparative response following infarction can be divided into three distinct, but overlapping, phases: the inflammatory phase, the proliferative phase, and the maturation phase [6]. During the inflammatory phase, danger signals released from necrotic cardiomyocytes trigger both systemic and myocardial inflammatory reactions, associated with induction of cytokines and chemokines, and subsequent mobilization of abundant neutrophils, monocytes, and lymphocytes that infiltrate the infarcted myocardium. Professional phagocytes clear the infarct from dead cells and matrix debris and undergo conversion to an anti-inflammatory phenotype that sets the stage for recruitment and activation of mesenchymal reparative cells, leading to the transition to the proliferative phase of healing [23–25]. During the proliferative phase of cardiac repair, activated myofibroblasts infiltrate the infarct predominantly derived from resident fibroblast populations [26], and deposit large amounts of extracellular matrix proteins in the infarcted area. Recruitment and organization of the myocardial scar, containing aligned myofibroblasts, is critical for protection of the infarcted myocardium from catastrophic rupture and provides mechanical support attenuating chamber dilation [27]. At this stage, activation of angiogenic pathways promotes formation of neovessels, ensuring sufficient perfusion of the highly cellular and metabolically active infarct. The maturation phase follows, associated with cross-linking of the extracellular matrix and quiescence of fibroblasts that no longer exhibit myofibroblast characteristics [28], but serve a supportive role for the mature scar [29]. Tight temporal regulation, sequential activation, and spatial containment of the cellular events associated with cardiac repair are critical to protect the infarcted heart from adverse remodeling and from the development of heart failure. Although early inflammatory activation may be required for leukocyte-mediated clearance of the infarct from dead cells and debris and for stimulation of a reparative program, excessive, prolonged, or expanding inflammation may cause sustained tissue damage, promoting adverse remodeling and accentuating fibrosis, and causing dysfunction. Given

their critical role in regulating inflammation and repair, it is not surprising that several members of the chemokine family have been implicated in repair and remodeling of the infarcted heart, and in the pathogenesis of post-infarction heart failure. Most inducible chemokines are markedly upregulated during the inflammatory phase of cardiac repair and mediate recruitment and activation of leukocyte subpopulations. However, some members of the family exert important actions during the proliferative phase, modulating angiogenic and fibrogenic responses (Fig. 1).

Regulation of Chemokine Synthesis in the Infarcted Myocardium

Both CC and CXC chemokines are markedly upregulated during the inflammatory phase of infarct healing. Many different cell types, including activated monocytes, macrophages [30], and lymphocytes [31], cytokine-stimulated vascular endothelial cells [32, 33] and fibroblasts [34–36], and ischemic, hypoxic, or stressed cardiomyocytes [37–39] have been suggested to serve as a cellular source of chemokines in the infarcted heart. In the infarcted myocardium, necrotic and stressed/injured cells, and the damaged extracellular matrix, release bioactive mediators that act as danger signals, termed danger-associated molecular patterns (DAMPs). DAMPs bind to cognate pattern recognition receptors (PRRs) of the innate immune system on surviving parenchymal cells and infiltrating leukocytes to activate chemokine transcription.

Which DAMPs Stimulate Chemokine Synthesis Following Myocardial Infarction?

Although necrotic cardiomyocytes and damaged extracellular matrix can release a broad range of DAMPs, whether specific bioactive alarmins are responsible for chemokine upregulation in the infarct remains unknown. High mobility group box-1 (HMGB1) released by dying cells has been identified as a key

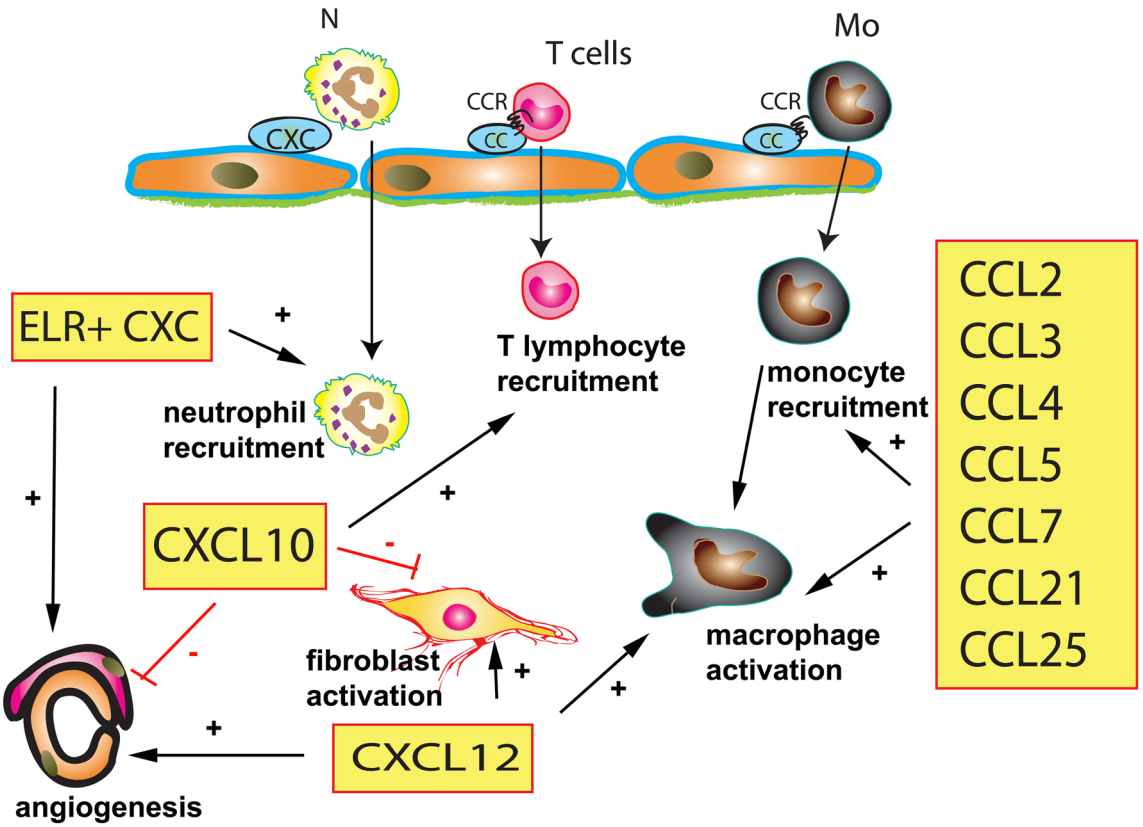

Fig. 1 The role of the chemokines in the infarcted myocardium. Induction of chemokines in the infarcted myocardium plays a critical role in leukocyte trafficking, but may also modulate phenotype and function of non-immune cells. Inflammatory CC and CXC chemokines bind to glycosaminoglycans on the endothelial surface and interact with leukocytes expressing the corresponding chemokine receptors. ELR+ CXC chemokines mediate neutrophil (N) infiltration, but may also act on the microvasculature (MV), exerting angiogenic actions. CXCL10 may act as an anti-fibrotic and angiostatic mediator. CXCL12 has been reported to exert a wide range of actions on leukocytes, cardiomyocytes, endothelial cells, and fibroblasts and may promote recruitment and differentiation of progenitor cells, stimulating angiogenesis. CC chemokines (including CCL2, CCL3, CCL4, CCL5, CCL7, CCL21, and CCL25) are involved in recruitment of mononuclear cell subpopulations and may modulate macrophage phenotype. Mo, monocyte

alarmin following myocardial infarction [40, 41], and can stimulate chemokine synthesis by endothelial cells [42] and fibroblasts [43] through activation of RAGE (receptor for advanced glycation end products). Necrotic cardiomyocytes also release large amounts of interleukin (IL)-1α [44], a key early damage signal that may stimulate chemokine synthesis in macrophages, vascular cells, and fibroblasts through MyD88-dependent signaling. RNA released by necrotic or injured cells also serves as an important pro-inflammatory stimulus in the infarcted heart [45], and may activate chemokine transcription. Heat shock proteins released by injured cardiomyocytes may also stimulate chemokine upregulation, contributing to activation of the post-infarction inflammatory response [46, 47] (Fig. 2).

Activation of Toll-like Receptor (TLR)-Mediated Pathways

DAMP-mediated chemokine induction in the infarcted heart involves activation of TLRs, the major PRRs on myocardial cells [48]. Following MI, TLRs expressed on leukocytes or parenchymal cells recognize DAMPs released by necrotic cells, triggering downstream NF-κB and MAPK pathways that stimulate chemokine induction. Experimental studies have suggested important roles for TLR2, TLR3, TLR4, and TLR7 in activation of the post-infarction inflammatory response. TLR4 signaling increased leukocyte infiltration in the infarcted myocardium [49–51], accentuating chemokine synthesis and release [52]. TLR4 activation in leukocytes has been consistently reported in patients with myocardial infarction and was associated with enhanced inflammatory activity [53, 54]. Leukocyte TLR2 has also been implicated in post-infarction inflammation [55], and may act, at least in part, through stimulation of chemokine synthesis [56]. TLR3 may also be involved in mediating chemokine-induced inflammation following myocardial infarction [45, 57]. Leukocyte TLR7 was also found to enhance post-infarction inflammation, promoting cardiac rupture following infarction [58], through actions that may involve increased chemokine expression [59]. It should be emphasized that the in vivo actions of TLRs in the infarcted heart extend beyond induction of chemokine synthesis and may also involve modulation of

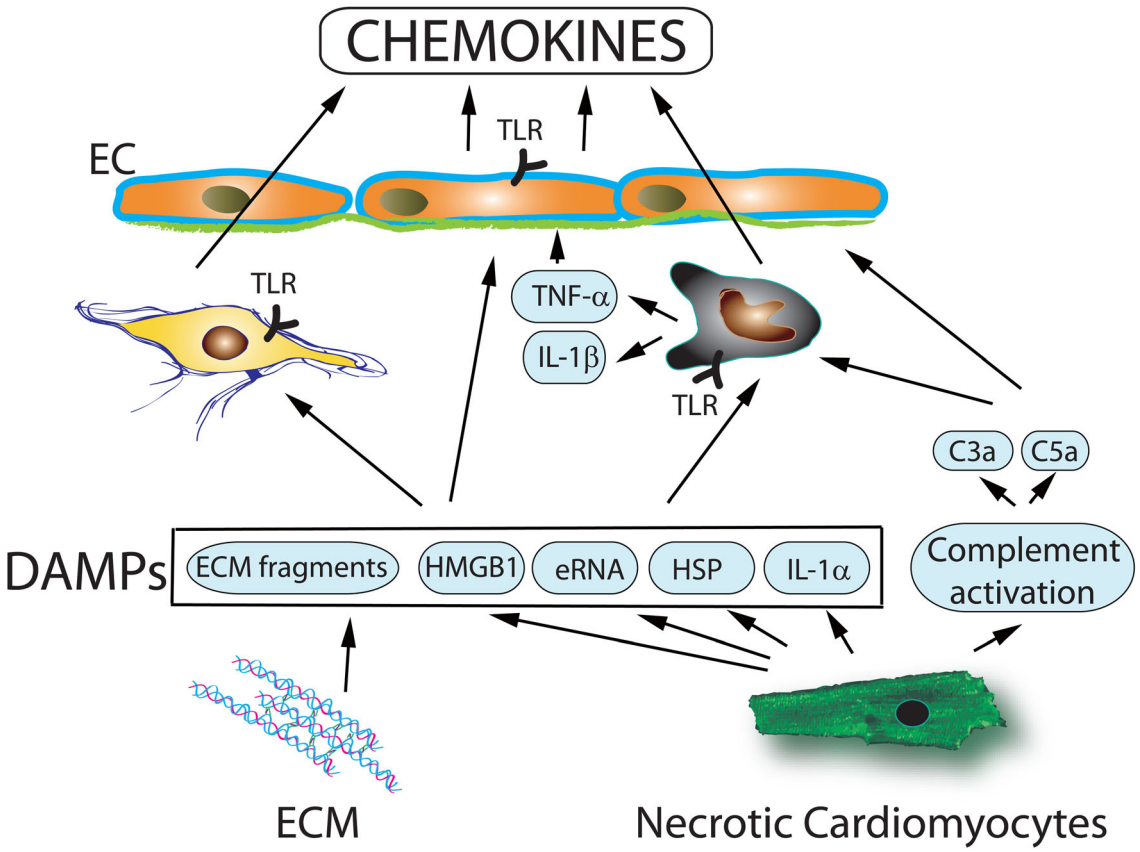

Fig. 2 Mechanisms of chemokine induction in the infarcted heart. Following myocardial infarction, dying cardiomyocytes release damage-associated molecular patterns (DAMPs) including high mobility group box-1 (HMGB1), heat shock proteins (HSP), extracellular RNA (eRNA), and interleukin (IL)-1α. DAMPs induce chemokine expression by endothelial cells (EC), macrophages, and fibroblasts through activation of innate immune pathways. Moreover, activation of the complement cascade, extracellular matrix (ECM) fragments generated through protease actions, and newly synthesized cytokines (such as TNF-α and IL-1β) also stimulate chemokine synthesis in the infarcted heart, promoting leukocyte infiltration. TLR, Toll-like receptor

cardiomyocyte survival [60] and effects on fibroblast phenotype and activity [61, 62].

DAMP-mediated TLR signaling triggers chemokine synthesis in the myocardium by activating the nuclear factor (NF)-κB system in resident myocardial cells and in hematopoietic cells. NF-κB activation in myocardial cells following infarction may involve an MyD88/IRAK-1 pathway [63] that ultimately leads to nuclear translocation of NF-κB and subsequent transcription of a large portfolio of genes including inflammatory cytokines, CXC and CC chemokines, and adhesion molecules. NF-κB activation is well documented following myocardial infarction in both experimental animals and human patients [64–66], and has been demonstrated to mediate upregulation of both CXC [65] and CC chemokines [67–70].

The role of the Complement Cascade in Stimulating Chemokine Synthesis in the Infarcted Heart

The complement system is an important component of the innate immune response following myocardium infarction. Necrotic myocardial cells release subcellular membrane constituents rich in mitochondria, which are capable of triggering the early acting components (C1, C4, C2, and C3) of the complement cascade [71]. Ischemic myocardial injury rapidly activates C3 cleavage leukotactic products in the infarcted myocardium [72]. In vitro studies have suggested that the pro-inflammatory actions of complement components (such as C5a) may be mediated at least in part through chemokine upregulation [73]. The role of the complement cascade in activating the chemokine response following myocardial infarction is supported by some limited in vivo evidence. C6-deficient rabbits exhibited reduced neutrophil infiltration following infarction, associated with attenuated myocardial CXCL8/interleukin (IL)-8 expression [74].

Cytokine-Induced Chemokine Upregulation in the Infarcted Myocardium

A large body of evidence suggests that induction of chemokines in the infarcted myocardium may be amplified by effects of pro-inflammatory cytokines, such as tumor necrosis factor (TNF)-α and interleukin (IL)-1β. TNF-α-deficient mice exhibit lower expression of chemokines and adhesion molecules after reperfused infarction [75]. Mice lacking the type I IL-1R (the only signaling receptor for IL-1) exhibit decreased chemokine expression associated with attenuated neutrophil and macrophage infiltration in the infarcted myocardium [76, 77]. In addition to the chemokine-inducing effects of pro-inflammatory cytokines, mast cell-derived pro-inflammatory mediators, such as histamine and tryptase, are also released in the infarcted myocardium [78] and can induce endothelial chemokine synthesis and secretion [79, 80].

The role of the Chemokines in myocardial Injury, Repair, and Remodeling

In the infarcted heart, the chemokine system orchestrates leukocyte migration [7, 8] by forming chemotactic gradients, which are localized to the area of injury. Gradient formation is dependent on binding of chemokines to glycosaminoglycans located on the endothelial surface and on the extracellular matrix. Endothelial chemokines interact with rolling leukocytes that express the corresponding chemokine receptors. Chemokine signaling promotes leukocyte integrin activation, triggering adhesive interactions between leukocytes and endothelial cells that ultimately lead to extravasation of the inflammatory cells in the infarct border zone [81, 82]. In extravasated leukocytes, chemokine:chemokine receptor interactions induce directed cell migration to the site of injury through activation of phosphoinositide-specific phospholipase C (PLC) and phosphoinositide 3-kinase (PI3K) pathways [83–85]. In addition to their effects on immune cells, some members of the chemokine family have been suggested to modulate behavior of other cell types involved in cardiac repair and remodeling, including vascular cells, fibroblasts, and cardiomyocytes [33, 86–88].

CXC Chemokines

ELR+ CXC Chemokines

ELR+ CXC chemokines not only are critically involved in chemotactic recruitment of neutrophils, but also exhibit angiogenic properties [89]. Several members of the ELR+ CXC subfamily are upregulated in the infarcted myocardium and have been suggested to play a role in neutrophil infiltration, regulation of cardiomyocyte injury, and angiogenesis. The prototypic ELR+ CXC chemokine CXCL8/IL-8 is markedly upregulated in infarcted myocardial segments in experimental animal models of myocardial infarction, and its expression is accentuated by reperfusion [90, 91]. Although as a potent neutrophil chemoattractant IL-8 would be expected to play an important role in recruitment of neutrophils in infarcted segments [92], robust experimental data documenting specific cellular actions of IL-8 in vivo are lacking. The absence of an IL-8 homolog in rodents precludes study of its role in myocardial infarction using mouse models. In a canine model, recombinant IL-8 markedly increased adhesion of neutrophils to isolated cardiomyocytes [90]. In contrast, an in vivo study in a rabbit model of reperfused myocardial infarction showed that administration of a neutralizing anti-IL-8 antibody prior to reperfusion reduced infarct size without affecting neutrophil infiltration [93]. Another study in mice suggested that effects on both leukocytes and cardiomyocytes may mediate the actions of ELR+ CXC chemokines in the infarcted heart. Loss of CXCR2, the main receptor for the ELR+ CXCLs, markedly

reduced inflammatory leukocyte recruitment in murine infarcts in vivo [87]; however, experiments in a Langendorff system suggested that, in the absence of circulating leukocytes, CXCR2 may protect ischemic cardiomyocytes [87]. In addition to their potential role in acute injury following myocardial infarction, IL-8 and other CXCR2 ligands may also modulate repair by exerting angiogenic actions. In a mouse model of myocardial infarction, CXCR2 blockade attenuated infarct angiogenesis [94]. Moreover, in a rabbit model, lentiviral IL-8 overexpression significantly enhanced neovessel formation in the infarcted heart [95].

A potential role of IL-8 in accentuating myocardial injury following infarction is also supported by clinical investigations. In patients with acute STEMI undergoing percutaneous coronary intervention (PCI), higher plasma IL-8 levels were associated with larger infarcts and adverse outcome [96].

ELR-Negative CXC Chemokines

In contrast to ELR-containing CXC chemokines, CXC chemokines lacking the ELR motif fail to attract granulocytes, but have been implicated in lymphocyte chemotaxis [97–99], and may exert pronounced effects on vascular cells and fibroblasts, exhibiting angiostatic and anti-fibrotic properties [100–102]. The ELR-negative CXC chemokine CXCL10/interferon-γ-inducible protein (IP)-10 is markedly upregulated in both canine and mouse myocardial infarcts [33, 103], and is predominantly localized in microvascular endothelial cells [33]. Experiments using global knockout mice suggested that endogenous CXCL10 protects the infarcted heart from excessive fibrotic remodeling, limiting infiltration of the infarct with activated myofibroblasts [86]. The anti-fibrotic effects of CXCL10 are mediated, at least in part, through inhibition of growth factor-induced fibroblast migration [86]. CXCL10-mediated inhibition of fibrosis was not mediated through CXCR3, the main functional receptor of the chemokine [104], but involved interactions with proteoglycans [105].

Stromal cell-derived factor (SDF)-1/CXCL12 is a non-ELR containing CXC chemokine with a critical role in cardiovascular development [106] and angiogenesis [107, 108]. CXCL12 induction is noted in healing infarcts [109–115] and has been suggested to exert a wide range of actions on vascular cells, cardiomyocytes, and immune cells. Extensive evidence suggested that CXCL12 accentuates infarct angiogenesis through recruitment of endothelial progenitor cells, or via direct stimulation of angiogenesis pathways [116–127]. Effects of CXCL12 on cardiomyocytes are controversial. Several studies have suggested protective actions of CXCL12 on cardiomyocyte survival, mediated through activation of anti-apoptotic pathways [122, 125, 128]. In contrast, other studies have suggested that high concentrations of CXCL12 may trigger apoptosis through a TNF-α-mediated pathway [88]. CXCL12-induced activation of inflammatory cells may also accentuate injury following infarction [129].

Experiments using pharmacologic inhibition of CXCL12 have also produced contradictory results (Table 1). Continuous inhibition of CXCR4, the main receptor for CXCL12, resulted in scar expansion and exacerbated cardiac systolic and diastolic dysfunction after myocardial infarction [130]. In contrast, other studies suggested beneficial effects of CXCR4 inhibition in rat and mouse models of myocardial infarction [131, 132]. The conflicting observations likely reflect the context and dose-dependent, multifunctional, and pleiotropic actions of CXCL12/CXCR4 signaling, and the complexity of the cardiac reparative process. Therapeutic manipulation of the CXCL12/CXCR4 axis following infarction requires careful consideration of the timing and spatial localization of the intervention, the specific cellular targets affected, and the local concentration of the chemokine. An additional layer of complexity may be contributed by effects of CXCL12 mediated through the CXCR7 receptor. CXCL12/CXCR7 signaling has been suggested to protect the infarcted heart from adverse remodeling, presumably through effects on the microvasculature [133].

Because of its prominent role in progenitor cell homing and differentiation [110], CXCL12 may hold promise in the ongoing quest for cardiac regenerative strategies. Although in adult infarcted hearts, CXCL12 overexpression does not induce cardiomyocyte proliferation [117], a recent study suggested that the unique ability of the neonatal mammalian heart to regenerate may involve CXCL12 actions. In neonatal myocardial injury, cardiac regeneration required CXCL12/CXCR4-dependent arterial reassembly, mediated through migration of arterial endothelial cells that formed collateral neovessels [134].

The Proinflammatory Actions of the CC Chemokines

Members of the CC chemokine subfamily are potent mononuclear cell chemoattractants and have been implicated in chemotactic recruitment of proinflammatory monocytes in the infarcted region [135]. CCL2/Monocyte chemoattractant protein (MCP)-1, the best-studied CC chemokine in myocardial pathology, is rapidly upregulated in the infarcted myocardium and is predominantly expressed by endothelial cells and infiltrating leukocytes [30, 32, 103, 136, 137]. Over the last 15 years, experimental studies in animal models have revealed a critical role for CCL2 in recruitment, activation, and differentiation of monocytes and macrophages in the infarcted heart (Fig. 3). These actions were found to have major implications in cardiac injury, repair, and remodeling.

The adult heart contains a significant population of resident macrophages [138]. Based on their expression of the CCL2 receptor CCR2, resident myocardial macrophages can be divided into CCR2− and CCR2+ subsets derived from embryonic and adult hematopoietic lineages, respectively

Table 1 Studies examining the role of the CXCL12/CXCR4 axis in myocardial infarction (MI)

MI model	Species	Experimental tool	Major findings	Ref.
Non-reperfused MI	Mouse	Conditional cardiomyocyte-specific CXCR4 −/− mouse models	Cardiomyocyte-specific CXCR4 loss did not affect infarct size, collagen content, and cardiac function following MI	[177]
Reperfused MI	Rats	Adenoviral CXCR4 overexpression	CXCR4 overexpression accentuated infarct size and worsened cardiac dysfunction following MI. These effects were associated with increased influx of inflammatory cells and enhanced cardiomyocyte apoptosis	[129]
Non-reperfused MI	Mouse	Cxcr4 +/− mice	CXCR4 +/− mice had smaller infarcts, associated with decreased neutrophil content, but also exhibited impaired angiogenesis following MI	[178]
Non-reperfused MI	Rat and mouse	Cardiomyocyte-specific CXCL12-overexpressing transgenic (Tg) rats and CXCL12 conditional knockout (cKO) mice	Cardiomyocyte-specific CXCL12 KO mice had preserved cardiac function, reduced remodeling, and attenuated fibrosis following MI CXCL12 overexpressing rats had impaired cardiac function post-MI, accompanied by enhanced fibrosis	[37]
Non-reperfused MI	Rats	Transplantation of CXCL12-expressing cardiac fibroblasts into the peri-infarct zone	Transplantation of CXCL12-expressing fibroblasts improved left ventricular function and increased left ventricular mass post-MI	[110]
Non-reperfused MI	Mouse	Injection of CXCL12 into the center of the infarct	CXCL12 treatment reduced scar size and improved cardiac function by promoting angiogenesis	[118]
Non-reperfused MI	Rat	Tail vein infusion of syngeneic CXCL12-overexpressing mesenchymal stem cells	Cell therapy with CXCL12-overexpressing MSCs increased cardiac myocyte survival, vascular density, and cardiac myosin-positive area within the infarct zone. There was no evidence of cardiac regeneration	[117]
Non-reperfused MI	Rat	Transplantation of CXCL12-expressing syngeneic skeletal myoblasts	Cell therapy with CXCL12-expressing myoblasts promoted stem and progenitor cell migration, activated cell survival signaling, and enhanced angiogenesis in the infarcted heart	[121]
Reperfused MI	Mouse	CXCL12 treatment prior to coronary ischemia Administration of the CXCR4 antagonist AMD3100	Pretreatment with CXCL12 decreased infarct size by inhibiting apoptosis in cardiomyocytes. CXCL12-induced attenuation of infarct size was blocked by CXCR4 inhibition	[128]
Non-reperfused MI	Rat	Administration of the CXCR4 antagonist AMD3100	CXCR4 blockade reduced infarct size, improved systolic function, and partially suppressed the increased expression of atrial natriuretic peptide mRNA in the non-infarcted left ventricle	[131]
Non-reperfused MI	Mouse	Intracardiac CXCL12 administration	CXCL12 treatment attenuated dysfunction and decreased cardiac dilation after MI, promoting survival of cardiomyocytes, increasing infarct angiogenesis. These effects were attributed to enhanced Akt activation and accentuated VEGF expression	[116]
Non-reperfused MI	Mouse	Chronic administration of the CXCR4 antagonist AMD3100	CXCR4 blockade increased scar size and exacerbated cardiac systolic and diastolic dysfunction	[130]
Non-reperfused MI	Mouse	Acute or chronic administration of the CXCR4 antagonist AMD3100	Single-dose AMD3100 injection administered after the onset of myocardial infarction increased circulating endothelial progenitor cell (EPC) counts and myocardial vascularity, reduced fibrosis, and improved cardiac function and survival in mice. In contrast, continuous infusion of AMD3100 over a 2-week period worsened outcome following MI by blocking EPC incorporation	[132]
Non-reperfused MI	Rats	Sustained release of a CXCL12 analog from injectable hydrogels	Sustained release of CXCL12 analog enhanced endothelial progenitor cell chemotaxis, improved vascularity, ventricular geometry, ejection fraction, cardiac output, and contractility post-MI	[119]
Non-reperfused MI	Sheep	Injection of a CXCL12 analog in the infarct border zone	Treatment with the CXCL12 analog enhanced endothelial progenitor cell chemotaxis, increased capillary and arteriolar density, reduced infarct size, and attenuated dysfunction post-MI	[120]
Non-reperfused MI	Rat	Intracardiac administration of recombinant CXCL12, or infusion of anti-CXCL12 antibody	CXCL12 administration reduced cell apoptosis, increased vessel density, and improved cardiac function. Treatment with the anti-CXCL12 antibody had the opposite effects	[127]
Non-reperfused MI	Mouse	Intramyocardial injection of CXCL12	CXCL12 injection improved ventricular function, and increased border zone vessel density post-MI	[126]
Non-reperfused MI	Mouse	CXCL12-Annexin V fusion protein to localize CXCL12 in the area of necrosis	CXCL12-Annexin V treatment attenuated cell apoptosis, enhanced angiogenesis, reduced infarcted size, and improved cardiac function post-MI	[125]

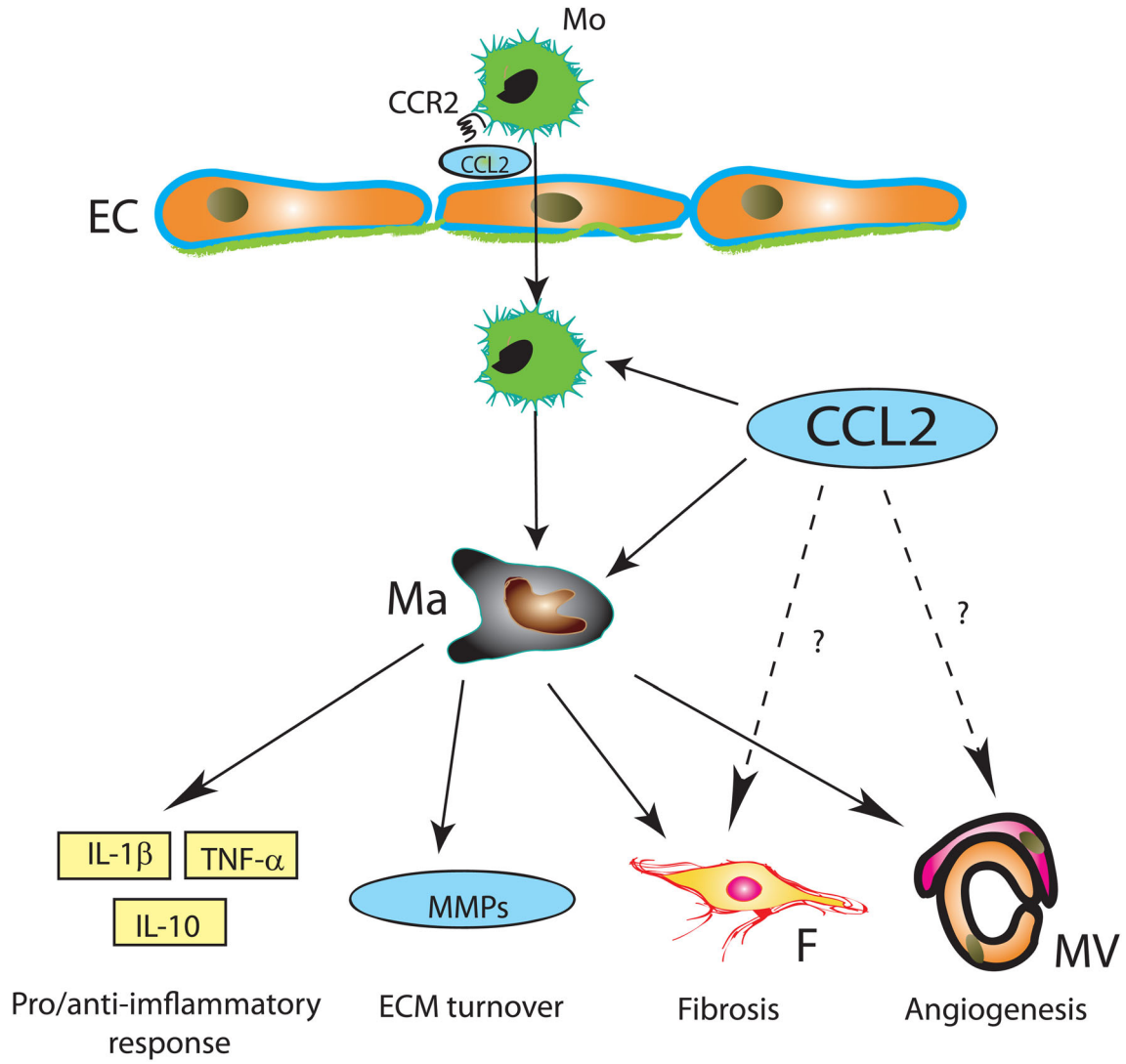

Fig. 3 Role of CCL2 in the infarcted myocardium. CCL2 plays a crucial role in recruitment of proinflammatory CCR2+ monocytes (Mo), but may also modulate macrophage (Ma) phenotype, promoting expression of cytokines and matrix metalloproteinases (MMPs). In vivo, CCL2 has been implicated in myofibroblast activation and in angiogenesis; however, whether these actions are due to direct effects of the chemokine on fibroblasts (F) and vascular cells (MV, microvessels), or simply reflect alterations in the profile of infiltrating macrophages, remains unknown. EC, endothelial cell

[139–142]. Cardiomyocyte death triggers alarmin-mediated activation of resident CCR2+ macrophages, stimulating MyD88-dependent chemokine synthesis [143] and subsequent recruitment of inflammatory leukocytes. Fate mapping and flow cytometric studies revealed that the marked expansion of the macrophage population in the infarcted myocardium is predominantly driven by recruitment of circulating monocytes [144]. During the proliferative phase of cardiac repair, proliferation of mature macrophages serves to maintain the infarct macrophage population [144, 145]. In the remodeling of non-infarcted myocardium, chronic expansion of macrophage populations is noted, derived both from increased local macrophage proliferation and through recruitment of monocytes [146].

The critical role of CCL2 in recruitment of monocytes and expansion of macrophages following myocardial infarction is supported both by antibody inhibition and by genetic loss-of-function experiments (Table 2) [135, 147–150]. Disruption of the CCL2/CCR2 axis in experimental models of myocardial infarction was reported to reduce infarct size in many [149–152], but not in all, studies [135]. Moreover, CCL2/CCR2 inhibition was associated with attenuated adverse remodeling following myocardial infarction [135, 153]. Importantly, in addition to its protective actions against dilative post-infarction remodeling, complete global loss of CCL2 also delayed replacement of dead cardiomyocytes with granulation tissue, suggesting impaired phagocytic removal of dead cells, and/or perturbation of the reparative response

Table 2 Selected studies examining the role of CC chemokines in experimental myocardial infarction (MI)

Chemokine/ chemokine receptor pair	MI model	Species	Chemokine-related model	Major findings	Ref.
CCL2/CCR2	Non-reperfused MI	Mouse	CCR2−/− mice	CCR2 loss impaired infiltration of macrophages in infarcted tissue, reduced infarct size and collagen deposition, and ameliorated post-MI remodeling	[153]
	Reperfused MI	Mouse	CCL2 −/− mice, anti-CCL2 antibody	CCL2 −/− mice exhibited decreased and delayed macrophage infiltration in the healing infarct and delayed replacement of injured cardiomyocytes with granulation tissue; decreased mRNA expression of the cytokines TNF-α, IL-1β, TGF-β2, TGF-β3, and IL-10; diminished myofibroblast accumulation, attenuated left ventricular remodeling, but similar infarct size when compared with wild-type animals. Infarct angiogenesis was comparable between CCL2 −/− and wild-type animals. CCL2 antibody inhibition resulted in defects comparable with the pathological findings noted in infarcted CCL2−/− animals without an effect on macrophage recruitment, suggesting that CCL2 may modulate macrophage phenotype or may alter the profile of recruited cells	[135]
	Reperfused MI	Mouse	CCR2−/− mice	CCR2 loss reduced macrophage infiltration and decreased infarct size	[179]
	Non-reperfused MI	Mouse	CCR2 antagonist and CCR2−/− mice	CCR2 disruption decreased monocyte/macrophage and neutrophil recruitment	[149]
	Reperfused MI	Rat	Intravenous injection of anti-CCL2 antibody	CCL2 blockade reduced infarct size and decreased intercellular adhesion molecule (ICAM)-1 mRNA expression and infiltration of macrophages	[136]
	Non-reperfused MI	Mouse	Anti-CCL2 gene therapy	Anti-CCL2 therapy reduced post-MI mortality and attenuated dilative remodeling and contractile dysfunction, reducing interstitial fibrosis, recruitment of macrophages, and myocardial cytokine gene expression	[180]
	Reperfused MI	Mouse	Cardiac-specific CCL2 overexpression	Transgenic overexpression of CCL2 attenuated post-MI dysfunction	[181]
	Reperfused MI	Mouse	Administration of a non-agonist (competitive) CCL2 mutant	CCL2 inhibition reduced infarct size, decreased monocyte infiltration, and attenuated fibrosis post-MI	[147]
	Reperfused MI	Mouse	CCR2-siRNA knockdown in Ly-6C^{high} monocytes	CCR2 inhibition reduced infarct size and attenuated infiltration of the infarct with monocytes and macrophages	[151]
	Reperfused MI	Mouse	Anti-CCL2	Reduced the infarct size and lessened myocardial inflammation	[148]
	Non-reperfused MI	Mouse	CCR2 siRNA	Decreased early infiltration of pro-inflammatory monocytes and apoptotic cardiomyocytes in the infarcted heart; promoted angiogenesis and reduced infarcted size	[152]
	Non-reperfused MI	Mouse	CCR2 antagonist	CCR2 inhibition reduced infarct size, decreasing recruitment of Ly6C^{high} inflammatory cells	[150]
CCL7/CCRs	Non-reperfused MI	Rat	Transplantation of CCL7 (MCP-3)-expressing cardiac fibroblasts into the infarct border zone	Transplanted CCL7-expressing cells enhanced homing of injected mesenchymal stem cells in the infarcted myocardium, reduced cardiac dilation, and improved cardiac function	[159]
	Non-reperfused MI	Mouse	B cell-selective CCL7 deficiency	Loss of CCL7 in B cells reduced monocyte mobilization, limited myocardial injury, and improved heart function post-MI	[31]
CCL5/CCRs	Non-reperfused MI	Mouse	Rat anti-mouse CCL5/ RANTES mAb	Anti-CCL5 reduced infarct size, reduced infiltration with neutrophils and macrophages, and attenuated systolic dysfunction	[160]
CCLs/CCRs	Non-reperfused MI	Mouse	Treatment with the CC chemokine binding protein evasin-4	The CC chemokine inhibitor reduced macrophage and neutrophil recruitment and superoxide production in the infarcted heart, reduced infarct size, and improved cardiac function and survival	[164]
CCL21/CCR7	Non-reperfused MI	Mouse	Anti-CCL21 monoclonal antibody	Anti-CCL21 diminished neutrophil and macrophage recruitment in the infarct; and ameliorated cardiac dilation and dysfunction post-MI	[162]
CCLs/CCR1	Non-reperfused MI	Mouse	CCR1 −/− mice	CCR1 loss reduced early recruitment of neutrophils, but also accelerated monocyte/lymphocyte infiltration and improved infarct healing	[165]
CCLs/CCR5	Reperfused MI	Mouse	CCR5 −/− mice	CCR5 loss markedly increased proinflammatory cytokine and chemokine levels in the infarct associated, perturbing	[167]

Table 2 (continued)

Chemokine/ chemokine receptor pair	MI model	Species	Chemokine-related model	Major findings	Ref.
				recruitment of CD4+/foxp3+ regulatory T cells and anti-inflammatory monocytes; impaired repression of post-MI inflammation was associated with worse cardiac dilation	
	Non-reperfused MI	Mouse	CCR5 −/− mice	CCR5 loss impaired macrophage activation, increased collagen fragments, and aggravated post-MI cardiac remodeling	[168]
	Reperfused MI	Rat	Anti-CCR5 antibody and CCR5 agonist	CCR5 inhibition diminished inflammatory response and infarct size, while CCR5 agonist accentuated cardiac injury	[182]
CCLs/CCR9	Non-reperfused MI	Mouse	CCR9 −/− mice	CCR9 loss attenuated inflammation, apoptosis, and structural and electrical remodeling through suppression of NF-κB and MAPK signaling. CCR9 loss also improved survival rate and attenuated dysfunction, decreasing infarct size	[161]

[135]. CCL2 actions in cardiac repair and remodeling may involve several cellular mechanisms. First, CCL2 may be crucial for recruitment of specific subsets of proinflammatory and phagocytic monocytes to the infarct area [135, 154]. Second, CCL2 may modulate macrophage phenotype. In vitro studies have suggested diverse and often contradictory effects of CCL2 on monocyte and macrophage cytokine expression profiles. CCL2 induced IL-1 [155] and IL-6 synthesis [156] in monocytes, but was also found to suppress M1-associated cytokine synthesis by macrophages, while promoting IL-10 expression [157]. Third, at least some of the effects of CCL2 may involve actions on fibroblasts, cardiomyocytes, or vascular endothelial cells. Although in vitro studies have demonstrated effects of CCL2 on interstitial and vascular cells, the in vivo significance of these actions remains poorly documented. In vivo, CCL2 loss markedly reduced myofibroblast density in the infarct [135]; however, this effect may reflect attenuated activation and recruitment of fibrogenic macrophages, rather than loss of direct effects of CCL2 on cardiac fibroblasts. In vitro, CCL2 stimulation did not affect expression of fibrosis-associated genes by isolated mouse cardiac fibroblasts [158].

Evidence supporting the role of other CC chemokines in repair and remodeling of the infarcted heart is more limited. In experimental models, CCL3, CCL4, CCL5, CCL7, CCL21, and CCL25 were found to be significantly upregulated in infarcted myocardium [31, 103, 159–162]. Moreover, small clinical studies have demonstrated increased circulating levels of CC chemokines in patients with myocardial infarction [163]. CCL5 neutralization significantly reduced infarct size and attenuated systolic dysfunction in a mouse model of non-reperfused infarction [160, 164]; considering the negligible amounts of salvageable myocardium in permanent coronary occlusion models (due to the complete and permanent absence of perfusion), the mechanism of protection remains enigmatic. Deletion of CCR1, a receptor binding to CCL3, CCL5, CCL7, and CCL23, loss of CCR9, the receptor for CCL25, and CCL21 inhibition were also reported to reduce the size of the infarct, decrease inflammation, and attenuate dysfunction following myocardial infarction [161, 162, 165].

Do CC Chemokines Mediate Suppression of Inflammation by Recruiting Anti-inflammatory Leukocytes?

CCR5 acts as a receptor for several CC chemokines, including CCL3, CCL4, and CCL5 [166]. Surprisingly, in a mouse model of myocardial infarction, CCR5 loss was associated with accentuated adverse remodeling and increased inflammatory activity [167, 168]. Adverse outcome in the absence of CCR5 was attributed to impaired recruitment of anti-inflammatory monocytes and regulatory T cells (Tregs) [167]. These findings suggest that certain chemokine-chemokine receptor interactions may attenuate inflammation by promoting recruitment of leukocyte subsets with anti-inflammatory properties.

The Role of CX3CL1/Fractalkine

Fractalkine/CX3CL1, the only member of the CX3C chemokine subfamily, is expressed by NK cells, monocytes, and T cells and has unique functions, both as a leukocyte chemoattractant and as an adhesion molecule. Increased myocardial CX3CL1 expression has been reported in infarcted and remodeling hearts [169, 170]. Moreover, in human patients with myocardial infarction, circulating CX3CL1 levels rapidly increase after reperfusion [171], and may independently predict major adverse cardiac events [172]. CX3CL1 neutralization delayed the progression of left ventricular enlargement following myocardial infarction [169, 173]. CX3CL1-mediated post-infarction remodeling has been attributed to accentuation of fibroblast proliferation [173], to enhanced MMP expression, to injurious effects on cardiomyocytes, to accentuated endothelial adhesion molecule expression [169], and to increased leukocyte recruitment [174].

Chemokines as Therapeutic Targets Following Myocardial Infarction

Considering their marked induction in the infarcted myocardium and their proposed role in mediating inflammatory injury, proinflammatory chemokines, such as CCL2, are attractive therapeutic targets for patients with myocardial infarction. It should be emphasized that some chemokine-driven inflammation and macrophage activation is needed for clearance of the infarct from dead cells and for activation of a reparative program [135]. However, the chemokine response needs to be tightly controlled. Prolonged, overactive, and spatially unrestrained chemokine signaling following infarction may result in accentuated inflammation, promoting adverse remodeling. Therapeutic implementation of chemokine targeting approaches will require identification of patient subpopulations with overactive chemokine responses following infarction. These patients may require chemokine inhibition to protect the myocardium from adverse remodeling [175].

Chemokine-based therapeutics may also hold promise in optimization of cardiac repair. CXCL12 administration may promote recruitment of reparative cells, increasing infarct angiogenesis, attenuating dysfunction, and improving left ventricular mechanics [116, 119, 120, 128]. Experimental studies suggest that pro-survival effects of CXCL12 on ischemic cardiomyocytes may also contribute significant therapeutic benefit [116]. Despite these promising findings, clinical translation is challenging. CXCL12 is also known to exert proinflammatory actions [131, 132] that may have injurious consequences, accentuating or prolonging inflammatory cascades. Identification of the optimal temporal window for spatially restricted administration of CXCL12 may be important in order to design effective therapy. Clinical evidence on the effects of CXCL12 therapy in human patients with myocardial infarction is lacking. However, in a phase II clinical trial in patients with ischemic heart failure, CXCL12 gene therapy was safe but did not meet the primary endpoint for functional improvement [176].

Conclusions

Over the last 25 years, we have identified members of the chemokine family as key mediators in cardiac injury, repair, and remodeling. Experimental studies have suggested that certain chemokines may represent attractive therapeutic targets for patients with myocardial infarction. Unfortunately, the biological complexity of the chemokine system, the challenges in identification of reparative and detrimental cellular function of each chemokine, and the remarkable pathophysiologic heterogeneity of post-infarction cardiac remodeling in human patients pose major challenges for clinical translation. Development of successful therapeutic approaches targeting the chemokines will require not only understanding of the cell specific actions of chemokines in the infarcted heart and the underlying mechanisms, but also development of strategies for pathophysiologic stratification of myocardial infarction patients, in order to identify subjects with overactive myocardial inflammation that may be likely to benefit from targeted interventions inhibiting proinflammatory chemokines.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

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