Int J Clin Exp Med 2011;4(1):74-80
www.ijcem.com /ISSN:1940-5901/IJCEM1101003

Review Article

Chemokines and inflammation in heart disease: adaptive or maladaptive?

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Received January 10, 2011; accepted February 3, 2011; Epub February 6, 2011; published February 28, 2011

Abstract: Heart disease is not only the leading cause of death, disability, and healthcare expense in the US, but also the leading cause of death worldwide. Therefore, treatments to lessen ischemia-related cardiac damage could affect a broad swath of the population and have significant health and fiscal impacts. Cardiac dysfunction has been associated with elevated circulating chemokine levels, both in animals and humans. Most studies in this area have focused on chemokine expression as a prominent feature of the post-infarction inflammatory response. Such studies have investigated the role of chemokines in inflammatory leukocyte recruitment. Other work on this topic has focused on stem-cell therapy or factors e.g. chemokines mobilizing bone marrow progenitor cells as possible avenues for improving contractile dysfunction. Findings from numerous preclinical studies and several initial clinical trials support the feasibility of promoting the recruitment of bone marrow-derived cells to the infarcted heart and increased homing following injury, supporting the notion that cell therapy might have therapeutic potential. They have not, however, addressed the possibility of an autocrine/paracrine effect wherein the chemokine receptors, present on the cardiac myocyte surface, modulate functional responses to stress in which can be adaptive or maladaptive in nature.

Keywords: Chemokines, stem-cell therapy, inflammation, myocardial infarction, congestive heart failure

Introduction

Coronary artery disease (CAD) is a leading cause of death in the United States. Acute myocardial infarction (MI) is a catastrophic manifestation of CAD that strikes nearly one million Americans each year. One fourth of afflicted patients die and many survivors develop impaired functional status, anginal symptoms, and diminished quality of life [1, 2]. The mainstay of current therapy in acute MI is the restoration of blood flow (*reperfusion*) to the affected area via thrombolytic therapy or an-gioplasty. Many studies have demonstrated clinical benefit from early reperfusion [3, 4]. However, reperfusion is itself associated with an inflammatory response and cardiac myocyte damage, called ischemia-reperfusion (I/R) injury. Thus, while the net result of early reperfusion is beneficial, an in-depth understanding of the complexity of the myocardial inflammatory response, including a determination of the cell type involved, is required to optimize current treatment strategies and to develop better ones. In addition, cardiac myocytes themselves may play a key role in the reperfusion process, as suggested by recent studies. For example, some work suggests that cardiac myocytes can both generate and respond to inflammatory responses, in an autocrine or paracrine manner, by modulating their contractile responses [5, 6] . We will describe the documented or hypothesized role of cytokines, in particular, chemokines, and their potential therapeutic role in the various pathogenesis steps of heart failure.

Cytokines, inflammation, and ischemic reperfusion injury

MI is associated with an inflammatory reaction, which leads to healing and scar formation [7]. Although inflammation can increase myocardial injury, an inflammatory response is a prerequisite for cardiac healing and scar formation.

However, chronic inflammation can lead to additional cell death and myocardial remodeling. Therefore, the extent of the inflammatory response may, in turn, be an important determinant of the host's outcome [8,9]. One of the major therapeutic goals is to design strategies aimed at minimizing myocardial necrosis and optimizing cardiac repair following myocardial infarction. However, attempts to completely limit inflammatory response, for example with the use steroids, have failed to reverse cardiac dysfunction [10]. Cell-specific anti-inflammatory therapies have been more promising. Several studies have shown the benefits of neutrophil inhibition [11, 12], presumably through inhibiting reactive oxygen species (ROS) and endothelial activation [13]. Mast cells have also been implicated as a source of cytokines, notably an immunologically active pre-formed tumor necrosis factor (TNF)-α [14]. In clinical studies, there have been discrepancies as to the relationship between serum cytokine levels in patients with MI and clinical outcome. Several small studies have demonstrated a positive correlation between serum cytokine levels, such as TNF [15], and interleukin (IL)-6 [16-18] and the size and severity of the MI. Other studies have not supported a significant correlation between cytokine levels and MI severity [19, 20].

Yet with all the experimental evidentiary support for the importance of leukocyte infiltration in the initiation of the inflammatory cascade that results in myocardial ischemic injury, clinical data is lacking. There are large numbers of animal studies with various approaches to blocking neutrophils using anti-CD18, a key signaling receptor in lymphocyte adhesion and a very efficient neutrophils paralyzing agent, has showed benefit in animal models of reperfusion injury. However, Genentech's phase II clinical trials to treat acute MI using anti-CD18 monoclonal antibodies, have failed to yield clinical benefits [21]. This is similar to what was observed in the heart failure trials that used "targeted" approaches to neutralize cytokines such as TNF in patients with heart failure [22]. Two trial programmes (the RENAISSANCE and RECOVER trials) testing an anti-cytokine medication in chronic heart failure (CHF) were halted because these targeted approaches resulted in worsening clinical outcomes, thereby raising important questions about what role, if any, proinflammatory cytokines play in the pathogenesis of heart failure [23, 24]. Recent studies have implicated a previously unexplored class of receptors, namely chemokine receptors, as direct mediators of myocardial function and potentiators of the cardiac myocytes response to ischemic stress [5, 6]. Chemokines are member of the cytokines family; however, given the substantial structural and functional differences between cytokine receptors and chemokine receptors, it is likely that modulation of chemokine receptors will have different effects than those seen with cytokines and their receptors.

Chemokines and chemokine receptors

Chemokines are small glycoproteins that stimulate leukocyte migration to sites of an inflammatory or immune response. Four chemokine subfamilies (CXC, CC, C and CX3C) are classified based on their primary amino acid sequences [25]. Chemokines function as ligands for G protein-coupled receptors (GPCR), which are seven transmembrane-spanning receptor proteins. Chemokine receptors differ both structurally and functionally from their cytokine receptor cousins such as TNFR and IL-2R. Cytokine receptors typically act via "horizontal" receptor signal transduction, wherein receptor molecules diffuse within the membrane plane. Binding of cytokines alters the association between receptor molecules that often cross the membrane only once in a single alpha-helical segment; consequently, the association of protein domains inside the membrane is altered as well. Signals thus are transduced by changes in oligomeric state of the receptors. These receptors, as a rule, exist in an "off-state" before activation [26].

In contrast, chemokine receptors function as "vertical" receptors [27] wherein the initial agonist-receptor interaction changes the receptor conformation transmitted vertically through the membrane. These receptors often respond to small ligands that cause a transient and reversible change in membrane potential or in cellular metabolism. The preassembled and generally unimolecular nature of these receptors allows them to respond rapidly. The different nature at many levels of cytokine and chemokine receptors suggests strongly that their functions in the cardiac response to inflammation are likely to be quite different. Therefore, the investigation of cardiomyocytes chemokine receptors is likely to yield novel insights into the myocardial inflammatory response.

Chemokines and heart disease

Cardiac dysfunction as been associated with elevated circulating chemokine levels in both animals and humans [28-30]. One of the first chemokines to be detected in the myocardium in response to I/R injury was Interleukin-8 (IL-8), a CXC chemokine, (CXCL8) [31]. It was hypothesized that IL-8 participates in the neutrophil-induced myocardial injury. Several other chemokines have been detected early in the hearts in animal models of injury [32]. These include CCL2 (Chemokine (C-C motif) ligand 2; also known as monocyte chemoattractant protein (MCP-1)), and CXCL10 (also known as Interferon-γ inducible Protein-10 (IP-10)). Almost all such chemokine studies have focused on their expression as a prominent feature of the post-infarction inflammatory response and therefore considered just the chemokines' role in inflammatory leukocyte recruitment [8]. These studies have not addressed possible autocrine/paracrine effects wherein the ligand-activated chemokine receptors, present on the cardiac myocyte surface, modulate functional responses to stress in the myocytes themselves.

The identification of functional chemokine receptors on cardiac mycoytes opened up a new line of research bridging the areas of immunology (i.e. chemokines) and cardiovascular biology. Once thought to be present only on inflammatory cells, chemokine receptors are now recognized biological effectors on cardiac myocytes as well. Among the chemokine receptors found on cardiac myocytes are macrophage inflammatory protein-2 (MIP-2) receptor, CXCR2, monocyte chemeoattractant protein -1 (MCP-1) receptor, CCR2, and most notably stromal derived factor-1 (SDF-1 also known as CXCL12) receptor,CXCR4 [6, 33]. They are for the most part constitutively continuously expressed but are upregulated following oxidative stress, both *in vivo* and *in vitro*. Furthermore, MIP-2 protein appears to induce the expression of MCP-1, a putative protector cardiac myocytes from hypoxia-induced apoptosis *in vitro*. It is noteworthy that in an animal model of I/R injury, the protective effect of MCP-1 was masked as a result of the recruitment of inflammatory cells in this model [33-35]. This is an example of how direct actions of chemokines on cardiac cells have been missed by the recruitment of inflammatory cells as seen in this model.

More recently, several groups have studied the effects of SDF-1-CXCR4 [36-40] in injury models. CXCR4 over-expression *in vivo* worsened cardiac function in an animal model of I/R injury. This deleterious effect of CXCR4 over-expression *in vivo* following I/R may result in part from the observed increase in production of its ligand (SDF-1). Over-expression of myocardial CXCR4 also leads to enhanced recruitment of inflammatory cells, increased TNF-α production and cell death/apoptosis [5]. These studies suggest that under conditions of stress, the paracrine and/or autocrine activation of CXCR4 by its ligand may trigger intracellular signaling pathways that exacerbate contractile dysfunction. One such pathway that may be affected is the beta-adrenergic signaling system. LaRocca et al. recently showed a clear interaction between CXCR4 and Beta-2 adrenergic receptor and that CXCR4 activation can interfere with Beta-adrenergic receptor downstream signaling [41]. Beta-adrenergic signaling plays a central role in the neuro-humoral regulation of the heart and the progression of heart failure. Given the central role of Beta-adrenergic signaling in progression of heart failure, further studies to unmask the potentials of CXCR4 in modulating disease pathophysiology are underway.

Chemokines and cell therapy

One potentially promising strategy for repairing damaged cardiac tissue following MI involves the use of cell therapy [42-46] to prevent or reverse heart failure [47]. Efforts in this area began with studies using already committed cells such as skeletal myoblasts [48], but recently a diverse range of cell types have been tested, including bone marrow (BM)–derived hematopoietic cells [49, 50], EPCs [44], mesenchymal stem cells (MSCs) [51], resident cardiac stem cells [43, 52], and embryonic stem cells. (ESCs) [53]. A related strategy for cardiac repair involves the testing of cell mobilization with factors such as cytokines—e.g., with granulocyte-colony stimulating factor (G-CSF) (the MAGIC cell randomized clinical trial) [54]. Several laboratories have shown that the cells can be mobilized and can home to areas of injury, in part in response to SDF-1/CXCR4 interaction [55] .

Given SDF-1's essential role in BM homing and recruitment [45,56], SDF-1 has been tested in gene therapy as a recruiter of BM-derived SC to the myocardium, in a murine infarct model [57-59]. SDF-1, acting through, CXCR4, did indeed recruit BM-derived cells to the injury, supporting

the notion that this chemokine might have therapeutic potential. Several clinical trials in this area have been recently been completed or are still ongoing. For example, a human trial – the REGENT trial -- was designed to assess the value of infusing either selected CXCR4-positive stem cells or non-selected BM mononuclear cells (BM MNC) in myocardial regeneration [60]. The objective of REGENT was to determine the effect of intracoronary infusion of selected population of autologous BM-derivedCD34+CXCR4+ progenitor cells compared with non-selected BM MNC on LV function in patients with acute ST-segment elevation MI and reduced left ventricular ejection fraction (LVEF). In patients with acute MI who developed impairment of the LVEF despite timely and successful treatment with primary percutaneous coronary intervention (PCI), treatment with BMCs (neither selected nor non-selected) did not led to a significant improvement of LVEF. Another phase 1 trial, which is currently underway, is examining the effects of SDF-1 on infarcted hearts. In this study, the ligand is injected directly into the heart and then monitoring homing of BMCs into the myocardium of patients with ischemic heart disease. Also noteworthy is an open-label dose-escalation study to evaluate the safety of a single escalating dose of SDF-1, administered by endomyocardial injection to cohorts of adults with ischemic heart failure, which is currently enrolling patients. In this study, naked DNA that encodes SDF-1 is being injected directly into the myocardium as a single dose at multiple sites through a percutaneous, left ventricular approach, using a needle injection catheter (ClinicalTrials.gov identifier: NCT01082094). These on going trials will demonstrate the safety and efficacy of using chemokines e.g. SDF-1 in SC therapies to treat heart failure in subjects with ischemic cardiomyopathy.

Open questions

Our understanding of the role of the SDF-1/CXCR4 receptor system in the heart failure has been hampered, however, by the lack of information about the cardiac myocytes expression/function of CXCR4 and SDF-1 during the various pathogenesis steps of heart failure. The cellular expression patterns of SDF-1 and the CXCR4 receptor can both generate inflammatory responses, in an autocrine or paracrine manner, and effect the cardiac myocytes adaptive signaling mechanisms e.g. contractile responses after ischemia. However, most if not all of these approaches have additional direct effects on the homing of BMCs into the myocardium of patients with ischemic heart disease and it is difficult to determine the beneficial contribution of chemokines cell mobilization from those associated with inflammation and/or contractile dysfunction. Based on the possible pathogenic role of chemokines in the development and progression of heart failure, many investigators have focused on myocardial gene expression and cellular localization of chemokines and their corresponding receptors in various stages of heart failure.

In summary, chemokine receptors such as CXCR4 belong to the GPCR family, and like other members of this family, are accessible targets for drug development [61,62]. CXCR4, like many GPCRs, exhibits heterogeneity of expression in different tissues and cell types, thus providing some selectivity (in some cases, specificity) in the targeting of these receptors for the activation or blockade of physiological events [63]. As a class, GPCRs have been the most successful molecular drug targets in clinical medicine. Agonists and antagonists of GPCRs are used to treat diseases of every major organ system including the CNS and cardiovascular systems. Additionally, the discovery of functional chemokine receptors on cardiac myocyte has broad implications for optimization of pre-existing chemokine/chemokine receptor-based SC therapies for ischemic cardiomyopathy.

Acknowledgments

The author apologizes to many colleagues whose work could not be cited because of space limitations. This publication was supported in part by National Institutes of Health grant 1K02HL102163, and American Heart Association grant 10GRNT4180006.

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