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EDITORIAL REVIEW

Chemokines in myocardial failure – pathogenic importance and potential therapeutic targets

P. AUKRUST*†, J. K. DAMÅS†‡, L. GULLESTAD‡ & S. S. FRØLAND*† *Section of Clinical Immunology and Infectious Diseases, †Research Institute for Internal Medicine, Medical Department and ‡ Department of Cardiology, Rikshospitalet, Oslo, Norway

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INTRODUCTION

Chemokines are small peptides that are potent chemoattractants for different leucocyte subpopulations and also have biological effects on certain other cell types such as endothelial cells, fibroblasts and vascular smooth muscle cells [1]. The chemokine superfamily is divided into four groups (CXC, CX_3C, CC and C) according to the relative positioning of the first two closely paired and highly conserved cysteines of the amino acid sequence [1]. Their actions are mediated by a family of seven-transmembrane spanning, G-protein-coupled receptors, the size of which has grown considerably in recent years and now includes 18 members [2]. A major role of chemokines is the recruitment and activation of specific subpopulations of leucocytes, playing a pivotal role in the immune response and inflammation. While chemokine-dependent functions are essential for the control of infection, wound healing and haematopoiesis, excessive chemokine activation may result in inappropriate inflammation leading to cell and tissue damage. Thus, chemokines have been suggested to play a pathogenic role in several immune-mediated and inflammatory disorders such as bronchial asthma, inflammatory bowel disease, rheumatoid arthritis, allograft rejection, encephalomyelitis and infection with human immunodeficiency virus [1,2]. Recently, chemokines have also been implicated in the pathogenesis of several cardiovascular disorders.

Chemokines – established pathogenic role in atherogenesis

The involvement of chemokines in the pathogenesis of atherosclerosis has been widely investigated and raised chemokine levels have been found both in plasma and in the atherosclerotic vessel itself. Thus, raised plasma levels of several chemokines (e.g. interleukin (IL)-8, monocyte chemoattractant protein (MCP)-1 and macrophage inflammatory protein (MIP)-1α) have been found in patients with coronary artery disease, with the highest levels in those with acute coronary syndromes [3]. Moreover, enhanced expression of several chemokines (e.g. IL-8, MCP-1 and interferon inducible protein 10 (IP-10)), has been found in human atherosclerotic lesions, possibly mediating chemoattractant and mitogenic effects on neutrophils, T cells and smooth muscle cells [4,5]. Furthermore, macrophages with enhanced expression of chemokine receptors (e.g. CXCR2 and CCR2) have been reported in advanced murine and human atheroma [4]. Also, knock-out mice lacking these receptors or their corresponding ligands (i.e. IL-8 and MCP-1) have significantly reduced progression of atherosclerosis [6–8].

Correspondence: Pål Aukrust, Section of Clinical Immunology and Infectious Diseases, Medical Department, Rikshospitalet, Sognsvannsveien 20, N-0027 Oslo, Norway.

E-mail: pal.aukrust@rikshospitalet.no

Chemokines and their receptors – possible involvement in the pathogenesis of myocardial failure

In the present issue of *Clinical and Experimental Immunology*, Fuse *et al*. [9] add further support to the notion that chemokines may also be involved in the pathogenesis of myocardial failure by demonstrating that high plasma levels of MCP-1 are associated with a fatal outcome in patients with acute myocarditis. Previously, raised serum levels of chemokines have been found in patients with chronic congestive heart failure (CHF) resulting from both ischemic and nonischemic cardiomyopathy, with the highest levels present in those with the most advanced disease [10,11]. Moreover, we have recently demonstrated expression of several chemokines and their receptors in the failing myocardium, with particularly enhanced expression of the chemokine receptors CXCR4 and CCR2 (i.e. the receptors for stromal cell-derived factor 1 and MCP-1, respectively) [12]. These human data are supported by animal studies demonstrating myocardial upregulation of chemokines such as MCP-1 in animal models of acute and chronic heart failure as also demonstrated by Fuse *et al*. in rat hearts with experimental autoimmune myocarditis [9]. In the latter study increased mRNA expression of MCP-1 was demonstrated in the myocardium during experimental autoimmune myocarditis and located to infiltrating mononuclear cells in the myocardial interstitium. However, enhanced myocardial chemokine expression has been found not only in animal models of autoimmune or viral induced myocarditis, but also in cardiac decompensation secondary to pressure-overload or ischemia [13–15]. Also, various studies using knock-out or transgenic mouse models have supported an important role for chemokines in the pathogenesis

of heart failure. Thus, interstitial monocyte infiltration in the myocardium with development of a number of pathological changes characterizing CHF, including cardiac hypertrophy, ventricular dilatation and depressed contractile function, is found in transgenic mice with myocardial over-expression of MCP-1 [16]. Moreover, MIP-1α knock-out mice do not develop cardiac lesions after Coxsacie B virus infection because of attenuated recruitment of activated monocytes into the myocardium [17]. Finally, the observation of high embryonic mortality and developmental defects, including cardiac ventricular septum defects in CXCR4 knock-out mice indicates a crucial and direct role for chemokines in the development and the function of the myocardium [18].

Chemokines in heart failure – mechanisms of action

Chronic low-grade inflammation with infiltrating leucocytes has been found in the failing human myocardium [19]. By playing a crucial role in recruitment and activation of these cells, chemokines may indirectly lead to damage and dysfunction of the cardiac muscle through activation and production of reactive oxygen species (ROS), matrix metalloproteinases (MMPs) and inflammatory cytokines [1,2,20]. In particular, although several cytokines may prime phagocytes for enhanced ROS generation, only certain chemokines (e.g. MCP-1 and IL-8) may directly induce ROS generation as has been found in CHF patients [10]. Moreover, several studies have demonstrated that oxidative stress may activate the transcription factor NF-κB in various cell types which again may induce the synthesis of IL-8 and MCP-1 possibly representing a pathogenic loop in CHF [10,21,22]. Furthermore, enhanced MMP activity and selective upregulation of MMPs have been found in nonischemic and ischemic forms of cardiomyopathy possibly contributing to myocardial remodeling [23], and chemokines such as MCP-1 and IL-8 may well be involved in this process [24]. Besides chemotaxis and leucocyte activation, chemokines may also regulate several other biological processes of importance to the pathogenesis of heart failure, e.g. fibrosis, angiogenesis and apoptosis [1,2,25,26]. Notably, increased cardiomyocyte gene expression of the MCP-1 receptor (CCR2) has been demonstrated in the failing human myocardium, suggesting that MCP-1 may play a pathogenic role in heart failure by directly acting on cardiomyocytes [11]. Indeed, we have recently shown that MCP-1 stimulates the release of other inflammatory cytokines (i.e. IL-1β and IL-6) in adult rat cardiomyocytes [27]. Thus, chemokines may potentially modulate myocardial function both directly through effects on cardiomyocytes and indirectly through effects on infiltrating leucocytes, fibroblasts or endothelial cells within the failing myocardium. In particular, the enhanced myocardial expression of chemokines and their corresponding receptors on both cardiomyocytes and infiltrating leucocytes in various forms of myocardial failure suggests a potential central role for chemokine–related interactions in the pathogenesis of these disorders.

Chemokine network – new targets for therapy in myocardial failure?

Despite 'state-of-the-art' cardiovascular treatment, CHF is a progressive disease with high mortality and morbidity, suggesting that important pathogenic mechanisms remain active and unmodified by the present treatment modalities. Persistent immune activation and inflammation may represent such 'unmodified mechanisms'. Indeed, neither β-blockers nor angiotensin-converting enzyme inhibitors seem to have any profound effects on inflammatory cytokines in CHF patients [28,29] and forms of immunomodulatory therapy, in addition to conventional cardiovascular treatment regimens, have therefore emerged as possible new and promising treatment modalities in these patients. Preliminary reports suggest that TNFα inhibition may have beneficial effects on cardiac performance in CHF [30], and immunomudulation with intravenous immunoglobulin or pentoxifylline has been suggested to enhance left ventricular function in both ischemic and non-ischemic cardiomyopathy [31,32]. The capacity to control activation and movement of inflammatory cells suggests that chemokines and their receptors might provide novel targets for therapeutical intervention in a number of diseases characterized by chronic inflammation. A series of chemokine antagonists have been found to prevent the development of several inflammatory diseases in animal models [33,34]. Our recent knowledge of the possible pathogenic role of chemokines in acute and chronic myocardial failure suggests that modulation of the chemokine network may represent interesting novel therapeutic modalities in these disorders also.

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