Fractalkine: a novel cardiac chemokine?

S.E. Altin and P.C. Schulze*

Division of Cardiology, Department of Medicine, Center for Advanced Cardiac Care, Columbia University Medical Center, 622 West 168th Street, PH 10, Room 203, New York, NY 10032, USA

This editorial refers to ‘Detrimental effect of fractalkine on myocardial ischemia and heart failure’ by W. Xuan et al., pp. 385–393, this issue.

The endothelium plays a central role in maintaining cardiovascular integrity, function, and the response to injury. A multitude of bioactive molecules is known to be expressed in and secreted from the endothelium under both physiological and pathophysiological circumstances. Xuan et al.1 uncover a unique role for fractalkine (FKN), a novel membrane-bound chemokine that is mainly expressed in endothelial cells in myocardial ischaemia and heart failure (HF). FKN, also known as CX3CL1, is an atypical chemokine that exists in either a membrane-bound form or as a cleaved soluble chemokine.1 The membrane-bound form acts as an adhesion molecule and can enable leucocyte adhesion via binding to CX3CR1, expressed on monocytes, NK cells, and a small subset of T cells.2,3 Under inflammatory conditions, the membrane-bound form can be cleaved to release a soluble chemokine that functions as a chemoattractant for monocytes and T cells.4 FKN has been implicated in a number of disease states, including atherosclerosis,5 glomerulonephritis,6 and cerebral ischaemia.7 Although also expressed in cardiomyocytes, very little is known about the role of FKN in the setting of HF. Of note, Husberg et al.8 used microarray data in a murine model of ischaemic ventricular dysfunction and identified 14 genes previously unknown to have any association with HF, with FKN showing the strongest upregulation.

Xuan et al.1 hypothesized that soluble FKN is harmful to cardiac myocytes and that its functional inhibition is cardioprotective. They first tested this hypothesis in mouse models of HF [either transverse aortic constriction leading to pressure-overload hypertrophy and subsequent left ventricular (LV) dysfunction or a myocardial infarction model with left coronary artery ligation] and found that FKN expression in the failing murine myocardium is enhanced. Next, they hypothesized that there was an association between FKN expression and measures of HF in these mouse models. Their data suggest that FKN expression is positively correlated with worsening HF phenotypes, specifically reduced LV fractional shortening measured by echocardiography, pulmonary congestion measured by lung weight to body weight ratio, and higher ventricular strain measured BNP levels. From these findings, they concluded that induction of FKN is closely associated with progression of LV dysfunction. They then asked whether soluble FKN (s-FKN) has an effect on cultured cardiac cells and whether a FKN-neutralizing antibody abrogates functional changes in these HF models. In cultured cells, they found that exposure to s-FKN increased mRNA expression of ANP in cardiomyocytes, ICAM-1 in endothelial cells, and MMP-9, procollagens I/II, and TGF-β in fibroblasts and that in all these experimental in vitro settings pre-treating with a neutralizing antibody to the FKN receptor attenuated the FKN response. These experiments also revealed that the effects of FKN are not restricted to a single cell type but seem to affect all major cells of the heart. In vivo, treatment of with FKN-neutralizing antibodies decreased the progressive decrease in LV fractional shortening and worsening of LV enlargement, implicating partial rescue of LV dysfunction by neutralizing s-FKN. Further, 3 weeks after MI, the mice that received the neutralizing antibody had decreased hypertrophy (estimated by heart weight to body weight ratio), smaller infarct size, and decreased ICAM-1 immunostaining of vascular endothelium compared with injured mice that did not receive the antibody. In the pressure-overload model, treatment with FKN-neutralizing antibody decreased cardiac remodelling indicated by LV posterior wall thickness, LV diameter, extent of hypertrophy, perivascular and myocardial fibrosis, and decreased lung weight to body weight ratio as a surrogate for pulmonary congestion.

The underlying molecular signalling events induced by FKN stimulation in cardiomyocytes involve p38 mitogen-activated protein kinase (MAP kinase) with subsequent pro-apoptotic signalling, and both p38 inhibition as well as FKN receptor antibodies blocked the deleterious effect of s-FKN in vitro. In endothelial cells, FKN expression was induced by tumour necrosis factor-α (TNFα) or hydrogen peroxide stimulation, implicating cytokine stimulation and/or oxidative stress in this pathway. The authors conclude that a possible mechanism through which FKN is associated with cardiac damage is via cell death and a MAP kinase-dependent pathway.

Because of FKN’s unique dual function as a membrane-bound protein and soluble molecule, it can attract monocytes and promote direct adhesion to endothelial cells. Yoshimoto et al.9 showed that in glomeronephritis patients, more severe glomerular lesions showed higher FKN expression and CD16+ monocyte accumulation. Among the monocyte subsets, CD16+ monocytes are thought to be pro-inflammatory due to production of pro-inflammatory cytokines and little of anti-inflammatory IL-10 compared with CD14+ CD16− monocytes.10,11 Further studies should...
include a systematic evaluation of monocyte recruitment to areas of ischaemia/reperfusion damage in the vasculature through adhesion assays in vivo and in vitro. Such studies would allow the characterization of distinct monocyte subsets associated with enhanced FKN expression in inflammatory states; e.g. in response to TNFα. Further, clarifying the differential effects of oxidative stress and the specific reactive molecules involved will prove important to better characterize the FKN-associated cardiovascular signalling network.

Overall, the results published in this issue provide an exciting insight into the molecular mechanisms by which FKN participates in the pathogenesis of HF. This report convincingly shows that FKN is associated with the development of HF, that it may provide a novel biomarker for HF severity, and that by blocking s-FKN with a neutralizing antibody some of the detrimental effects of cardiac remodelling and extent of ischaemic injury are abrogated, both in vitro and in vivo. Therefore, FKN is both a novel marker and unique mediator of myocardial damage and remodelling.

**Funding**

P.C.S. is supported by grants from the NIH (K23 HL095742-01, P30 HL101272-01, UL1 RR 024156, HL073029) and the Herbert and Florence Irving Scholar Award. S.E.A. is supported by a T32 training grant from the NHLBI.

**Conflict of interest:** none declared.

**References**