Vascular Pharmacology 60 (2014) 1–7

Contents lists available at ScienceDirect

Vascular Pharmacology

journal homepage: www.elsevier.com/locate/vph

Review

Effects of interleukin-1 on cardiac fibroblast function: Relevance to post-myocardial infarction remodelling

Neil A. Turner *

Division of Cardiovascular and Diabetes Research, University of Leeds, Leeds, UK
Multidisciplinary Cardiovascular Research Centre (MCRC), University of Leeds, Leeds, UK

ARTICLE INFO

Article history:
Received 22 April 2013
Received in revised form 21 May 2013
Accepted 14 June 2013

Keywords:
Cardiac fibroblast
Myocardial infarction
Interleukin-1
Signal transduction pathways
Therapies

ABSTRACT

The cardiac fibroblast (CF) is a multifunctional and heterogeneous cell type that plays an essential role in regulating cardiac development, structure and function. Following myocardial infarction (MI), the myocardium undergoes complex structural remodelling in an attempt to repair the damaged tissue and overcome the loss of function induced by ischemia/reperfusion injury. Evidence is emerging that CF play critical roles in all stages of post-MI remodelling, including the initial inflammatory phase that is triggered in response to myocardial damage. CF are particularly responsive to the proinflammatory cytokine interleukin-1 (IL-1) whose levels are rapidly induced in the myocardium after MI. Studies from our laboratory in recent years have sought to evaluate the functional effects of IL-1 on human CF function and to determine the underlying molecular mechanisms. This review summarises these data and sets it in the context of post-MI cardiac remodelling, identifying the fibroblast as a potential therapeutic target for reducing adverse cardiac remodelling and its devastating consequences.

Contents

1. Introduction

Cardiac fibroblasts (CF) are the major cellular components of the heart, outnumbering cardiomyocytes by as many as 2:1 [8,37]. These multifunctional and heterogeneous cells play important roles in many aspects of cardiac structure and function including its

* Division of Cardiovascular and Diabetes Research, School of Medicine, Worsley Building, Clarendon Way, University of Leeds, Leeds LS2 9JT, UK. Tel.: +44 113 3435890; fax: +44 113 3434803.
E-mail address: n.a.turner@leeds.ac.uk.

1537-1891/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.vph.2013.06.002

embryonic development, normal physiology and pathophysiology [11,16,41,57,69,71]. CF are particularly important regulators of the myocardial extracellular matrix (ECM). As well as controlling synthesis of structural ECM components (e.g. collagens, laminins, fibronectin), CF are also a source of ECM-regulatory molecules including matricellular proteins (e.g. thrombospondins, CCNs, tenascins), matrix metalloproteinases (MMPs) and MMP inhibitors (TIMPs). The close proximity of fibroblasts to cardiomyocytes and other myocardial cell types facilitates inter-cellular communication via both physical interactions (e.g. gap junctions) and via local paracrine signalling networks (e.g. synthesis and secretion of growth factors and cytokines), and hence CF are able to influence multiple aspects of cardiac function.

CF are intrinsically involved in the complex structural remodelling of the heart that occurs following myocardial infarction (MI), as well as in other cardiac pathologies that can lead to heart failure including hypertension, cardiomyopathy and myocarditis [11,41,57,69,71]. Aspects of CF function that are particularly pertinent to myocardial remodelling include their ability to proliferate, migrate in response to chemotactic stimuli, differentiate into myofibroblasts, regulate ECM turnover and synthesise and secrete numerous autocrine/paracrine signalling molecules, including growth factors, angiogenic factors and inflammatory cytokines and chemokines [57].

Following MI, the myocardium undergoes complex structural remodelling in an attempt to repair the damaged tissue and to overcome the loss of function induced by ischemia/reperfusion injury [37]. Post-MI remodelling occurs through a highly organised series of events involving both resident myocardial cells and infiltrating extra-cardiac cells such as neutrophils, monocyte/macrophages and myofibroblast precursors. The post-MI healing process can be divided into three overlapping stages referred to as the inflammatory, granulation (proliferative) and maturation phases [30,73]. It is becoming increasingly apparent that CF are critically involved in all these stages of myocardial repair and remodelling.

2. Cardiac fibroblasts and post-MI remodelling

2.1. Inflammatory phase

Recent evidence suggests that CF can act as early triggers of the myocardial inflammatory response, preceding the infiltration of inflammatory cells [38]. Although cardiomyocytes undergo rapid necrotic cell death in response to ischaemia, CF appear to be less sensitive to oxygen and nutrient starvation [83] and could therefore be important sensors of early cardiomyocyte damage. The close positioning of myocytes and fibroblasts in the heart, coupled with recent evidence that CF express components of the innate immune system including Toll-like receptors and NOD-like receptors [28,60], suggests that fibroblasts are able to rapidly sense endogenous danger signals known as damage-associated molecular patterns (DAMPs) that occur following myocyte damage and necrosis [7,85]. Importantly, CF express a functional inflammasome that facilitates activation and secretion of the proinflammatory cytokine IL-1β [38]; one of the main triggers for the myocardial inflammatory response. In addition to IL-1β, CF are capable of secreting a host of other proinflammatory cytokines and chemokines including tumour necrosis factor (TNF)α, IL-6, IL-33, CC chemokines (e.g. CCL2/MCP-1) and CXC chemokines (e.g. CXCL1/GROα/KC and CXCL8/IL-8,) in a feed-forward loop driven by the inflammatory milieu, thereby exacerbating the initial inflammatory response [22,42,65–67]. Although further studies are required to determine the precise relative contribution of CF in this early inflammatory stage of remodelling compared with other cell types (mast cells, neutrophils, monocyte/macrophages, etc.), the available evidence to date suggests that CF play an important role [18].

2.2. Granulation phase

CF are also integrally involved in the granulation phase of remodelling, the transitional stage between inflammation and fibrosis [18,73]. Granulation tissue comprises mostly macrophages and myofibroblasts, the latter being derived from a variety of sources including resident CF, endothelial cells, epithelial cells, bone marrow-derived fibrocytes, pericytes and smooth muscle cells [41,82]. Myofibroblasts are a differentiated form of fibroblasts, characterised by increased alpha-smooth muscle actin (αSMA) expression, that are not present in the normal healthy myocardium [63,71]. In response to proinflammatory stimuli such as IL-1 and TNFα, myofibroblasts produce high levels of ECM-degrading proteases (especially MMPs) to degrade the damaged tissue prior to clearance by phagocytic leukocytes. This ECM degradation also facilitates (myo)fibroblast migration into the infarct area where they undergo increased proliferation in response to mitogenic stimuli, thus rapidly increasing local myofibroblast numbers. Neovascularisation is an important component of the granulation phase, and (myo)fibroblasts likely contribute to this through their ability to modulate endothelial cell function, for example through secretion of VEGF [84]. In addition to their effects on MMPs, proinflammatory cytokines such as IL-1 may also be important stimulators of VEGF secretion and activity at the level of the fibroblast [70].

2.3. Maturation phase

As the granulation phase progresses, increased levels of pro-fibrotic molecules (e.g. TGFβ, CTGF/CCN2), combined with a reduction in inflammatory signals (e.g. IL-1), drive a switch in myofibroblast function away from ECM degradation towards synthesis of structural ECM components (particularly collagen I and III) and scar formation [18,73]. Myofibroblasts are the most prevalent cell type in scar tissue and are the main effectors of fibrogenesis [55]. Their expression of contractile cytoskeletal proteins (e.g. αSMA) and focal adhesion proteins (e.g. paxillin, integrin αVβ3) enables mechanical contraction of the scar edges to facilitate wound healing and scar maturation [63].

2.4. Reactive fibrosis

Although myofibroblast numbers decrease rapidly after scar formation, they can persist in the healed scar for many years after MI [78] and may be important for maintaining the strength and flexibility of the scar [69,71]. However, persistent myofibroblast activation and continual local production of inflammatory cytokines, particularly in non-damaged areas of the myocardium (reactive fibrosis), can promote sustained inflammation, neurohormonal activation, ventricular wall stiffening, cardiac dysfunction and eventually heart failure [11].

3. Interleukin-1 and post-MI remodelling

3.1. IL-1 in the heart

The proinflammatory cytokine IL-1 comprises two distinct gene products (IL-1α and IL-1β) that have indistinguishable biological activities mediated via activation of the cell surface receptor IL-1R1 [6,26]. A third receptor ligand, IL-1RA (IL-1 receptor antagonist), is structurally related to IL-1α and IL-1β but acts as an inhibitor of IL-1 signalling as it binds to, but does not activate, the IL-1R1 receptor complex. Increased myocardial IL-1α/β levels are associated with many cardiovascular pathologies including MI, cardiomyopathy, hypertension and myocarditis [14,45]. As neither IL-1α nor IL-1β molecules possess leader sequences they are unable to be secreted from cells via the normal Golgi-mediated vesicular transport pathway.

IL-1α is an intracellular cytokine localised to the cytosol and also the nucleus where it appears to activate transcription of inflammatory genes [76]. IL-1α is only released from cells when they are