Pharmacological Research 101 (2015) 30–40

Contents lists available at ScienceDirect

Pharmacological Research

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

Review

Cardiac fibroblasts as sentinel cells in cardiac tissue: Receptors, signaling pathways and cellular functions

G. Díaz-Araya*, R. Vivar, C. Humeres, P. Boza, S. Bolivar, C. Muñoz

Laboratory of Molecular Pharmacology, Chemical Pharmacological and Toxicological Department, Faculty of Chemical and Pharmaceutical Sciences, FONDAP Advanced Center for Chronic diseases ACCDiS, University of Chile, Santiago, Chile

ARTICLE INFO

Article history:
Received 15 June 2015
Received in revised form 30 June 2015
Accepted 1 July 2015
Available online 4 July 2015

Keywords:
Cardiac fibroblast
Sentinel cells
Receptors
Cytokines
Cellular functions

ABSTRACT

Cardiac fibroblasts (CF) not only modulate extracellular matrix (ECM) proteins homeostasis, but also respond to chemical and mechanical signals. CF express a variety of receptors through which they modulate the proliferation/cell death, autophagy, adhesion, migration, turnover of ECM, expression of cytokines, chemokines, growth factors and differentiation into cardiac myofibroblasts (CMF). Differentiation of CF to CMF involves changes in the expression levels of various receptors, as well as, changes in cell phenotype and their associated functions.

CF and CMF express the β2-adrenergic receptor, and its stimulation activates PKA and EPAC proteins, which differentially modulate the CF and CMF functions mentioned above. CF and CMF also express different levels of Angiotensin II receptors, in particular, AT1R activation increases collagen synthesis and cell proliferation, but its overexpression activates apoptosis. CF and CMF express different levels of B1 and B2 kinin receptors, whose stimulation by their respective agonists activates common signaling transduction pathways that decrease the synthesis and secretion of collagen through nitric oxide and prostacyclin I2 secretion. Besides these classical functions, CF can also participate in the inflammatory response of cardiac repair, through the expression of receptors commonly associated to immune cells such as Toll like receptor 4, NLRP3 and interferon receptor. The activation by their respective agonists modulates the cellular functions already described and the release of cytokines and chemokines. Thus, CF and CMF act as sentinel cells responding to a plethora of stimulus, modifying their own behavior, and that of neighboring cells.

Contents

* Corresponding author at: Facultad Ciencias Químicas y Farmacéuticas, Universidad de Chile, Olivos 1007, Santiago 8380492, Chile.
E-mail address: gadiaz@ciq.uchile.cl (G. Díaz-Araya).

http://dx.doi.org/10.1016/j.phrs.2015.07.001
1043-6618/

1. Introduction

Cardiac fibroblasts (CF) represent about 2/3 of the cardiac cellular population, and play a relevant role in heart remodeling by regulating structural, biochemical, mechanical and electrical properties of the heart. Several reports describe the presence of different classes of receptors, the most important in the regulation of cardiac fibroblast cellular functions being the β2-adrenergic (β2-AR), angiotensin II (AT1R) and B1 (B1R) and B2 (B2R) kinin receptors and their corresponding signaling pathways. [1–7]. Essential functions in which CF are associated to cardiac remodeling and fibrosis are, cell proliferation, cell death by apoptosis, autophagy, migration, adhesion, secretion of extracellular matrix (ECM) protein, collagen gel contraction, CF differentiation to cardiac myofibroblasts (CMF) and finally cytokines and growth factors synthesis [8,9]
.

CF have gained increasing attention for their function as inflammatory supporting cells in a process, inflammation, that plays a significant role in the pathogenesis of cardiovascular diseases. Initially it was thought that inflammatory process were only attributable to immune cells, such as neutrophils and monocytes/macrophages. However, it is now known that others cells besides inflammatory cells are important players in cardiac inflammation. In this regard, the capacity of CF to respond in an efficient manner to pathogen-associated molecular patterns (PAMPs) or danger-associated molecular patterns (DAMPs) secreting a broad class of chemokines and cytokines, has refocused their role as sentinel cells in cardiac tissue, highlighting their important role in cardiac inflammation process [10], and also as cells that secrete cytokines and therefore, can modify the function of resident cardiac cell as cardiomyocytes, vascular smooth muscle cells and endothelial cells [11], as well as the activity of surrounding cells like immune cells [12].

2. Receptors, signaling pathways and cellular function

2.1. Adrenergic receptors

The adrenergic system plays, in physiological situations, a fundamental role in the regulation of the circulation [13]. All adrenergic receptors (alpha and beta) are present in the heart tissue. The β1-adrenergic receptor is the most important one in the heart, and leads to most of the actions of adrenergic stimulation in cardiac muscle cells [13–15]. In in vivo models, we and others have shown that treatment of rats with isoproterenol (a nonspecific β-adrenergic agonist), in a wide range of single or multi dose, induces both cardiac hypertrophy and fibrosis, without changes in blood pressure [16–19]. Isoproterenol produces a microinfarct-like cardiac lesion, and triggers inflammatory processes that lead to cardiac fibrosis, a process in which CF and CMF participate actively [20]. However, CF express exclusively the β2-AR, and its stimulation with isoproterenol induces several changes at molecular and cellular level regulating cell proliferation, collagen secretion, migration, adhesion and CF differentiation.

2.1.1. β2-adrenergic receptors in cardiac fibroblast and myofibroblasts

As mentioned before, CF only express the β2-AR (neither β1, α1/2 or muscarinic receptors are present in this type of cell) [1,15]. Such a situation has been observed in human CF obtained from right atrium, where only the β2-AR but not β1 is expressed [21]. This was elegantly demonstrated with the use of Isoproterenol, a non-selective β-agonist that increased cAMP through β2-AR, which was reversed by the use of β2-selective antagonist (ICI-118,551) but not by atenolol (β1 selective antagonist) [21]. In CMF, we have described the presence and function of this receptor, although its pharmacological characteristics do not change in relation to CF [3]. However, other groups have shown that fibroblasts treated for 24 h with TGF-β1 (TGF-β1 induces the differentiation of CF to CMF), exhibit a decrease in the expression of β2-AR [22], although it should be considered that treatment for 24 h with this cytokine is not enough to induce the differentiation from CF to CMF. The decrease in the number β2-AR in CMF could be beneficial under conditions of adrenergic overactivation (i.e., after cardiac infarction), since lower levels of cAMP could up-regulate the secretion of ECM proteins, which would imply a better healing process after cardiac injury.

2.1.2. Intracellular signaling pathways activated by β2-adrenergic receptor in cardiac fibroblasts

It is known that β2-AR stimulation increases cAMP levels, and that this second messengers can modulate the activity of both PKA and EPAC proteins which are responsible for many cellular responses, such as proliferation, differentiation, ECM protein secretion, migration and ion transport [23–26]. However, the activation of β2-AR also mediates cAMP-independent effects through the activation of ERK1/2, a critical signaling pathway for cell growth and protein synthesis [27]. In particular, CF expresses EPAC1 more abundantly than EPAC2, and it has been shown that TGF-β1 pro-

motes a decrease in the expression of EPAC1 (but not EPAC2) both at protein and mRNA expression level.

2.1.3. Effect of agonists and/or antagonists adrenergic on proliferation, secretion of ECM proteins, adhesion and migration in cardiac myofibroblasts

In CF, cAMP has been implicated as a critical modulator of proliferation [1], collagen synthesis inhibition [28], and as an inhibitor of lung fibroblast-mediated collagen gel contraction [29]. In this regard, the stimulation of β2-AR induces proliferation of human and rat CF, which depends on ERK1/2 activation [5,30]. In addition, another important effect of β2-AR activation is that it triggers CF autophagy, by a cAMP-dependent pathway, associated to a survival mechanism [5]. We showed that EPAC and PKA promoted CF and CMF adhesion on fibronectin, as well as CF migration; however, this effect was not observed in CMF [3]. In line with this observation, other studies have shown that PKA and EPAC differentially regulate migration and morphology of fibroblasts: the Epac-Rap1 pathway promotes migration and expression of fibrogenic morphology, whereas PKA inhibits migration and promotes a less fibrogenic morphology [31]. With respect to collagen synthesis, our data showed that EPAC and PKA activation reduce collagen synthesis in CF and CMF [3]; however, the overexpression of EPAC1 also inhibits collagen synthesis induced by TGF-β1, implying that a decrease in the expression of EPAC would be required for a profibrotic response, thus, indicating that EPAC plays a key role in integrating profibrotic and antifibrotic responses in fibroblasts [31]. In agreement with this hypothesis, it has been demonstrated that an increase in cAMP levels can inhibit the differentiation of CF to CMF caused by TGF-β1 [28,32]. We demonstrated that EPAC but not PKA activation mediated fibroblast collagen gel contraction; while in CMF collagen contraction was dependent on both PKA and EPAC.

There is little information on the effects of β2-AR antagonists in CF, and no information on its effects in CMF. Available data show that the β2-adrenergic receptor antagonist ICI 118.551 but not atenolol or other β1-adrenergic receptor blockers prevented proliferation induced by isoproterenol [21,30]. Furthermore, it was shown that carvedilol but not metoprolol reduced the secretion of collagen from CF isolated from infarcted and non-infarcted areas, but this effect was not due to its activity as a β-adrenergic blocker, but by its antioxidant effect [33]. Nonetheless, recent findings have shown that β-adrenergic blockers promote skin wound regeneration, mainly through its activity as β2-AR antagonist in dermal fibroblasts [34,35], increasing the secretion of collagen and favoring migration.

2.1.4. Adrenergic receptors and cytokines release in CF

To date, inflammation after cardiac injury is an interesting topic of research [8,36,37]. In this process, there is abundant evidence about the different cytokines released by cardiac myocytes or CF, in terms of type, quantities released and stimulus that promotes their synthesis and secretion [8,11]. However, the data about the participation of β2-AR to cytokines release by CF is scarce. In this regard CF, but not cardiomyocytes, serve as the predominant source of IL-6 after isoproterenol stimulation in mouse myocardium [38,39]. Mouse CF treated with isoproterenol showed a time-dependent accumulation of IL-6, which was mediated by an increase in cAMP levels induced by β2-AR activation; however, neither PKA nor EPAC were involved in such increase. The authors suggest the possible intervention of other signaling pathways that could explain this process, such as the MAPK p38. These findings open the possibility of a novel and noncanonical cAMP responsible pathway mediated by p38 MAPK [39].

2.2. Angiotensin receptors

The Renin–angiotensin–aldosterone system (RAAS) regulates blood pressure and extracellular corporal volume. Angiotensin II (Ang II) is the main RAAS effector; it has many physiological functions which are increases in ACTH secretion, aldosterone synthesis and secretion, Na^+ tubular reabsorption and regulation of blood pressure [40]. In hypertensive hearts, Ang II induces cell growth, promoting cardiac fibrosis [41]. Ang II activates two receptors, AT1R and type II receptor (AT2R) to perform its physio-pathological functions. Both receptors belong to the superfamily of G protein coupled receptors [42].

2.2.1. Ang II receptors in cardiac fibroblast and myofibroblasts

CF express both AT1R and AT2R [6,43], and AT1R activation induces cell proliferation and increases ECM proteins synthesis [44]. Hypertension or cardiac infarct promotes the increase in CF AT1R expression, which is associated with cardiac fibrosis [45]. AT2R effects in CF are unclear. Data from our laboratory indicate that AT2R is expressed in CF, but its overexpression does not induce changes in cell viability [6]. Similar results were obtained in porcine CF, where AT2R does not modulate cell proliferation, collagen I expression and ERK1/ERK2 activity [46]. In CMF, radioligand binding studies demonstrated that these cells expressed a single class of high affinity Ang II AT1R; whereas CMF from the infarct area revealed a lower maximal binding capacity, compared to sham operated myocardium. Conversely, CMF from remote area had a higher expression of Ang II AT1R mRNA compared to CMF from sham operated [47].

2.2.2. Angiotensin receptors signaling-pathways in cardiac fibroblasts

Ang II binding to its specific receptor AT1R promotes activation of various signaling pathways; being phospholipase C and protein kinase C the most studied ones. Bai et al. demonstrated that Ang II induces CF differentiation into CMF and calphostin C (PKC inhibitor) abolished Ang II effect [48]. Data from our laboratory indicate that the overexpression of AT1R in CF caused apoptosis induced by Ang II. This effect was inhibited when CF were incubated with U73122 (a PLC inhibitor) and Gö6976 (a PKC inhibitor), whereas AT2R overexpression had no effect on CF [4]. AT1R activation is also involved in the increase of reactive oxygen species (ROS) through NADPH oxygenase [49], an effect implicated in the development of cardiac fibrosis and hypertrophy [50]. This association can be explained by the fact that Ang II induces cardiomyocyte hypertrophy through NADPHox activation [51], whereas in CF, Ang II promotes ROS increase through NADPHox activation and triggers proliferation and collagen I synthesis. These effects were prevented by losartan (AT1R antagonist) [50]. In CF, AT1R activation also promotes MAPK signaling-pathway activation, which induces CF proliferation; PD98059 (a MEK-ERK inhibitor) blocked Ang II effect [52]. In atrial CF Ang II induced CTGF expression (profibrotic factor), which was suppressed by the AT1R antagonist losartanas well as a p38 MAPK inhibitor (SB202190), ERK1/2 inhibitor (PD98059) and the JNK inhibitor (SP600125) [53]. Finally AT2R generally exerts actions which are opposite to those of AT1R, mainly through nitric oxide production and activation of phosphatases that inhibit MAPK functions [54]. AT2R signaling-pathways activated in CF are not fully elucidated.

2.2.3. Effect of AT1R activation on proliferation, secretion of ECM proteins, adhesion and migration in cardiac myofibroblasts: a key event in promoting cardiac fibrosis

CF functions associated to cardiac fibrosis development have been studied in different experimental models. Proliferation and collagen synthesis were increased, and migration and adhesion

decreased in CF isolated from cardiac infarcted area but not in those from remote regions [55]. The importance of AT1R in cardiac fibrosis has been demonstrated in some studies, which show that ACE inhibitors and AT1R antagonists abolish cardiac fibrosis promoted by hypertension or myocardial infarct. In CF, AT1R activation induces TGF-β1 synthesis and secretion, and losartan decreases collagen I synthesis and CF differentiation to CMF induced by Ang II [56]. CTGF is a TGF-β1 effector that is highly expressed in cardiac fibrosis, and its expression is associated with CF differentiation and cardiac fibrosis [57–59]. Ang II also plays a critical role in CF adhesion [60], since integrin expression are upregulated by Ang II, and this effect was associated to increases in FAK activity [61]. Another important CF function that is regulated by Ang II is cell migration, which is a key process in wound healing. Siddesha et al. reported that Ang II promotes CF migration by suppressing the MMP regulator "reversion-inducing-cysteine-rich protein with Kazal motifs" (RECK), through a mechanism dependent on AT1R, ERK MAPK, and Sp1 [62]. Cardiac fibrosis relationship with AT2R seems less clear. AT2R expression is upregulated in failing hearts, and CF present in the interstitial regions are the major cell type responsible for its expression [63]. Furthermore, AT2R functions are controversial, as it effects on cardiac fibrosis remain to be elucidated [64,65]. However, recently Ocaranza et al. demonstrated that angiotensin-(1-9) promotes beneficial effects in hypertensive rats, such as cardiac dysfunction and fibrosis decrease. This latter protective effect of angiotensin-(1-9) was blunted by coadministration of the AT2R blocker PD123319 [66].

2.2.4. Angiotensin receptors and cytokines release in cardiac fibroblasts

Formerly, in the heart the CF were simply considered as supporting cells, whose main known function was to regulate ECM integrity. However, it is now known that CF exhibit different types of receptors that allow them to respond to pathological stimuli. In damaged cardiac tissue, TGF-β1 is initially secreted by inflammatory cells and then is synthesized and secreted by CF. TGF-β1 promotes anti-inflammatory effects, which favor tissue wound healing [8]. The more important stimulus that increases the synthesis and secretion of TGF-β1 is Ang II, through AT1R activation, which is associated to cardiac fibrosis and anti-inflammatory effects [56]. However, data demonstrate that AT1R promotes inflammation in heart tissue as well. Spontaneously hypertensive rats present tissue damages, with inflammatory zones, endowed with numerous inflammatory cells and high levels of proinflammatory cytokines, such as IL-1β and IL-6. Interestingly, captopril, an ACE inhibitor and losartan decreased these inflammatory markers, demonstrating that Ang II, through AT1R activation, is important to cardiac inflammation [67]. Furthermore, AT1R activation in mice promoted an inflammatory environment through TNF-α secretion and TNF-α receptors, which is linked to cardiac fibrosis and losartan prevented Ang II effects [68]. In this regard, it was observed that CF were the main cardiac cells responsible for TNF-α synthesis and secretion induced by Ang II, associated to cardiac fibrosis development [69].

2.3. Kinin receptors

Additional to the RAAS and in direct interaction with this system, the Kinin/Kallikrein system (KKS) also participates in the homeostasis of blood pressure and cardiovascular pathophysiology. All components of this system have been identified in the heart, including tissue kallikrein, kininogen, kinins and B1R and B2R [70–72]. Bradykinin (BK) and Lis-bradykinin (Lys-BK) [73] are agonists for the B2R, while des-Arg-BK (DABK) and Des-Arg-LysKD (DAKD) are agonists for the B1R [74]. BK and kallydin (KD) are inactivated by ACE, which removes the C-terminal of BK and KD, generating biologically inactive fragments. Moreover, BK and KD act locally and produce pain, vasodilatation, increased vascular permeability and synthesis of prostaglandins and nitric oxide [70]. The expression of B1R and B2R are increased after myocardial ischemia [71], and KO animals for the B2 receptor develop ventricular hypertrophy, myocardial damage and heart failure associated with fibrosis [75]. These findings support the idea that the absence of the B2R has a deleterious effect on the myocardium and therefore, reinforce the idea that the kinin/kallikrein system would have a protective effect by preventing the development of cardiac fibrosis.

2.3.1. Kinin receptors in cardiac fibroblasts and myofibroblasts

In physiological conditions, B2R is widely expressed and is the responsible for the action of kinins [76]; however, only a few cell types express B1R,which is increased pathological conditions such as ischemia, atheromatous disease or exposure to inflammatory cytokines [70,77,78]. Villarreal et al. identified B2R in rat and human CF [79], whereas Catalán et al. described the presence of both receptors in CF and in CMF; however, the expression levels for B1R were higher in CMF respect CF [7], whereas B2R expression was unaffected.

2.3.2. Kinin receptors signaling-pathways in cardiac fibroblasts

The intracellular signal transduction pathways activated by kinin receptors involves the activation of a variety of second messenger systems, depending on the cell type [76,80]. Kinin receptors are coupled to Gαi and/or Gαq proteins, which activates ionic channels (Ca^{2+}) as well as phospholypases C, A2 and D (PLC, PLA2 and PLD). The PLC generated products, such as inositol 1,4,5-triphosphate and diacylglycerol (DAG), activate protein kinase C (PKC), endothelial NO synthase (eNOS), and PLA2 [76], a system in which eNOS and PLA2 are responsible for the production of NO and prostaglandins (PGs) E2 and I2, respectively. In addition to these classical pathways, B2R can activate cytoplasmic signaling proteins endowed with tyrosine kinase activity [81], and the pathway of JAK/STAT in endothelial cells [82]. The B1R also interacts directly with Gαi and Gαq proteins, and shares the same signaling pathways of B2R, being principally associated with the activation of PLC, but also acting through PLA2 and MAP-kinases [76,74]. Although B1R and B2R appear to occupy similar signal transduction pathways, the cell signaling patterns differ in terms of variation and concentration of Ca^{2+} (in both duration and intensity) [83].

In CF BK activates the B2R and induces an increase in intracellular Ca^{2+}; whether this increase come from intracellular compartments or by external influx is not yet clear. Finally, BK activates iNOS and COX1 and COX2 leading to the production of NO and PGI2 [7]. Associated with these pathways we have also described that CMF do not express NOS, and only express COX2. Moreover, in CMF the intracellular signaling pathways activated by B1R and B2R converge to a same effect, because the activation of B1R and B2R by DAKD and BK, respectively, induced an increase in the concentration of intracellular Ca^{2+} [7].

2.3.3. Kinin effects on cell proliferation/cell death, migration, adhesion and ECM protein secretion in cardiac fibroblast and myofibroblasts

BK or DAKD did not show effects on CF and CMF proliferation and viability [7]. Similar results to this effect have also been assessed indirectly through the use of ACEi drugs. The effects of these drugs on apoptosis/proliferation are quite divergent and depend on the ACEi administered, experimental model and cell type evaluated. The anti-apoptotic effects of ACEi have been studied in vitro on cardiac myocytes [84], and in vivo in models of ischemia–reperfusion; these effects were blocked by coadministration of the B2R antagonist icatibant [85], indicating that the actions of ACEi may be mediated by kinins; the same anti-apoptotic effects of ACEi has been found in endothelial cells [86] and CF [87]. Various

mechanisms are responsible for these effects, including decreased levels of Ang II, the anti-oxidant effect produced by the increase of NO levels triggers by B2R activation, endothelin-1 reduced expression and the role of proinflammatory cytokines [88]. In CF and CMF the activation of B2R negatively modulates collagen secretion, an effect mediated by the release of NO and PGI2 [7,89,90]; however, only in CMF the activation of B1R decrease collagen synthesis. In CF the reduction of collagen secretion by BK was iNOS dependent, since both L-NAME (a pan NOS inhibitor) and 1400W (a specific iNOS inhibitor), prevented the reduction of collagen secretion. Similarly, indomethacin (a COX inhibitor) also prevented the reduction in collagen secretion levels, indicating that the secretion of PGs induced by BK is responsible for these effects. While, in CMF the effect of the stimulation of B1R and B2R led to a decrease in collagen secretion, and this effect was inhibited by indomethacin but not by L-NAME and 1400W. These results indicate that the decrease in collagen secretion is regulated by the same intracellular signaling pathways activated by B1R and B2R, but different from those in fibroblasts [7].

2.3.4. Kinin receptors and cytokines release in cardiac fibroblasts

There is no information about cytokines secretion induced after activation of B1R or B2R in CF and CMF. However, BK and DAKD induce the secretion of NO and PGs, which has a recognized role as proinflammatory signal [7]. Conversely, the available data indicate that IL-1β and TNF-α are the main inductors of B1R and B2R. In CF from normotensive Wistar-Kyoto (WY) and spontaneously hypertensive (SHR) rat, IL-1β increased B1R and B2R at similar levels; however, following IL-1β treatment, BK attenuated the turnover of ECM proteins in SHR but not WK cells, indicating that SHR cells are more susceptible to BK. In contrast, DAKD did show no significant effects in either cell [91]. Finally, there are no data regarding TNF-α effects on B1R or B2R expression in CF, although in dermal fibroblast TNF-α increased B1R, but B2R remained unchanged [92]. Thus, although CF and CMF do not secrete cytokines, these cells are target of cytokines which could affect in a different manner the cellular function associated to cardiac inflammation and fibrosis.

3. Receptors linked to inflammatory response in cardiac fibroblasts

Multiple families of germ-line encoded pattern-recognition receptors (PRRs) participating in the innate immune system participate actively to inflammation. To date, PRRs are divided into at least 4 distinct families: Toll-like receptors (TLRs), retinoic acid-inducible gene-I-like receptors (RLRs), C-type lectin receptors (CLRs), and the nucleotide-binding domain leucine-rich repeat containing receptors (NLRs; also known as Nod-like receptors). Of these, TLRs and NLRs are known to be involved in sterile inflammatory responses of myocardial infarct (MI) [93]. In the last few years, there has been great advance in the field of immune-cardiac system interaction. It has been extensively described that immune cells participate in most of cardiac pathologies associated to inflammation, such as myocarditis, MI and hypertension [94], through their ability to quickly adapt and communicate with cardiac cells. This highly regulated process allows cardiac resident cells, such as CF to participate actively in all phases of cardiac tissue repair as multipurpose cell. At first, CF promote the synthesis and release of inflammatory mediators while at later stages, tissue scarring and reparation are governed by CMF [93].

3.1. Toll-like receptors

Toll-Like Receptors (TLR) recognize and react to highly conserve structural motifs known as pathogen-associated microbial patterns (PAMPS), which are exclusively expressed by microbial pathogens or with danger-associated molecular patterns (DAMPs) released after cell death or tissue injury [95]. TLR4 has been one of the most studied receptors due to the accumulating evidence that describes its activation as a key element in the initiation and resolution of inflammatory responses [96]. TLR4 holds particular interest in cardiac inflammation, since it can also be activated by endogenous ligands such as heat shock protein (HSP), hyaluronate and fibronectin; all of which are released after tissue injury, which promotes a strong pro-inflammatory response via by the activation of inflammatory signaling pathways, release of cytokines and expression of cellular adhesion molecules [97].

3.1.1. TLR4 expression in cardiac fibroblasts

TLR4 is widely expressed in the myocardium and its levels increase in several models of heart infarct [98] . TLR4 knockout mice exposed to MI, exhibit less hypertrophy and adverse remodeling associated to a decrease in the infarct size and inflammatory response [99]. Whereas high levels of one of its ligand, HSP70, have been found in biopsies of patients after heart surgery, followed by a modest increase in proinflammatory cytokines [100]. While most of the studies have focused on the expression of TLR4 on immune cells recruited to the site of injury after MI [101], it is interesting to note that this receptor is also expressed in CF [102]. Considering the high diversity of receptors expressed by these cells and their involvement with cardiac pathologies, it seems evident that TLR4 should also play an important role in the modulation of adverse remodeling and fibrosis.

3.1.2. TLR4 signaling-pathways in cardiac fibroblasts

The stimulation of TLR4 facilitates the activation of two signaling pathways: (a) the MyD88 independent pathway, which activates IRF3 and leads to the production of type I interferon (IFN R), and (b) the MyD88-dependent pathway, involving early activation of NF-kB, inducing proinflammatory cytokine expression. By activation of the MyD88 dependent pathway, TLR recruits and activates various downstream kinases such as IRAk-1, IRAK-4 and others, via specific scaffold protein, which involves the activation and nuclear migration of NF-kB. However, it should be noted that other signaling pathways, such as MAPK and IFN are also involved in many of TLR4 responses [95] (See Fig. 1). In last years, the inflammatory role of CF has drawn attention as a possible therapeutic target, especially in the cytokine synthesis and release.

3.2. NLRP3 receptor and the inflammasome in cardiac fibroblasts

The inflammasome is a multiprotein complex extensively studied in the last decade. This complex consists of three different types of proteins. (1) Receptor protein, belonging to the PRR family receptor and responsible for the immune innate response to foreign pathogens and danger signals. The most studied receptor is NLRP and particularly NLRP3 (NALP3). DAMPs or PAMPs signals activate intracellular NLRP3 and induce its polymerization. (2) Adaptor protein, that is essential for receptor proteins that do not have a CARD domain for caspase binding,. These small molecules work as a link between the receptor protein and the effector protein. NLRP3 does not have a CARD domain and utilizes ASC as an adaptor. (3) Caspase-1 that acts as the the inflammasome effector protein. Normally this enzyme is inactive (pro-caspase-1), but when it is recruited by ASC is activated and cleaves pro-IL-1β into IL-1β.

The inflammasome system has a particular activation; it needs two signals, the first one is triggered by a PAMP or DAMPS that activates a PRR, like TLR, and concludes with the transcription and translation of pro-IL-1β and pro-IL-18, while the second one is triggered by specific molecules like ATP, nigecirin [102], monourate sodium uric (MSU) [103], cholesterol crystals [104] and silica [105], among others. These molecules activate, by a non-elucidated

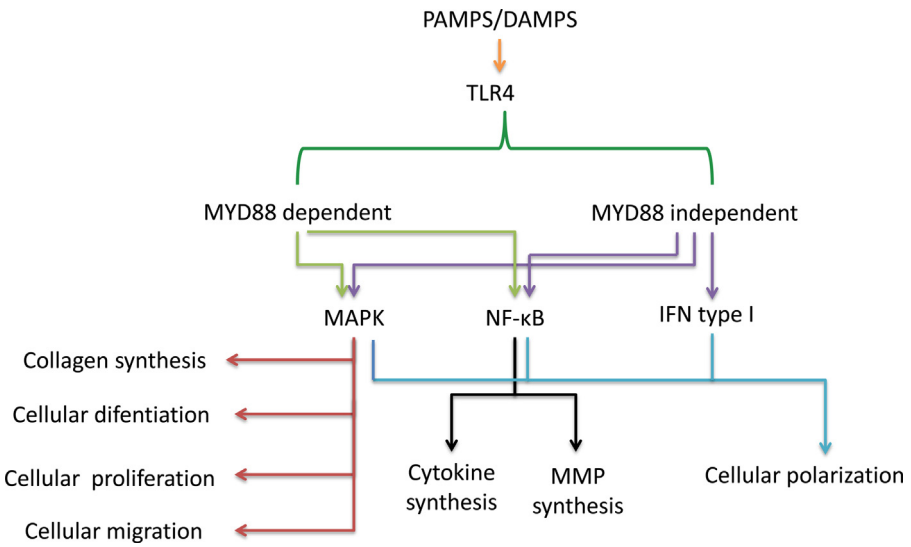

Fig. 1. TLR4Cardiac fibroblast signaling pathways associated to cardiac inflammation and fibrosis. Cardiac fibroblasts express TLR4 and its activation by DAMPS or PAMPs triggers MYD88-dependent and -independent signaling pathways. The MYD88-dependent pathway activates MAPK and NF-kB and controls cellular function associated to cardiac fibrosis or cardiac inflammation, whereas the independent pathway activates IFN type I, which is also associated to inflammation.

mechanism, the inflammasome assembly and the activation of caspase-1, leading to the cleavage and release of active IL-1β and IL-18. This inflammatory signaling has been widely studied in immune cells, but its role and function on cardiac cells has not been fully understood. CF are the main resident cells that release IL-1β during initial injury, initiating the immune phase [10]. These cells have similar inflammasome activation, which is activated by ATP but not by MSU [106]. Kawaguchi et al. described that CF inflammasome is an important mediator in ischemia and reperfusion, suggesting its potential therapeutic uses in MI [10]. In addition, in vivo experiments corroborated a marked increase in NLRP3, IL-1β, and IL-18 mRNA expression in the left ventricle after MI, primarily located on CF. Further, isolated CF released IL-1β and IL-18 when the cells were stimulated with LPS and ATP (mimicking a MI) [106].

CF inflammasome not only plays a critical role in models of inflammation caused by MI or I/R models. An animal sepsis model showed that there is a relation between endotoxemia and inflammasome NLRP3, caspase-1 and IL-1β in CF. Furthermore, the NRLP3 blockage with the sulfonylurea receptor 1 inhibitor glyburide or a NRLP3 siRNA prevented IL-1β release in isolated CF [12]. In addition, Bracey et al. reported that NLRP3-deficient CF displayed impaired differentiation and R-Smad activation in response to TGF-β1. This effect was independent of the role of inflammasome assembly in CF. These finding suggests that CF NLRP3 could also be related to CF differentiation [107]. Thus, the cardiac inflammasome is an active and it can be a novel target for cardiac disease.

3.3. Interferon receptors

Interferons (IFNs) are a family of cytokines that cause a myriad of biological responses, depending from the type of cell which they originate from [108]. IFNs are classified in IFN-type I (IFN-I) (with more than 20 subtypes including α, β, ϵ, ω, etc.), IFN-type II (IFN-II) or IFN gamma (IFN-γ) and the IFN-type III (IFN-III) or IFN lambda (IFN-λ). IFN-I can be produced by several cells from the innate immune system, including macrophages and dendritic cells, as well as in non-immune cells such as CF [109]. Their production is predominantly induced as an inflammatory response after the activation of several Toll-type receptors (TLRs) present in these cells [110]. IFN-γ is only produced by immune cells, such as natural killer cells (NK) and T cells after the cytokine stimulus, such as IL-12 [108].

3.3.1. Interferon receptor and canonical transduction pathway

All IFN-I subtypes are recognized by a common receptor, composed by the IFNAR1 and IFNAR2 sub-units [111], while IFN-γ joins the IFN-II receptor, composed by two subunits, IFNGR1 and IFNGR2 [112]. The different subtypes of IFNs share some common transduction pathways, such as its canonical signaling pathway, Janus kinase (JAK)/signal transducer and activator of transcription (STAT); therefore, they activate some common genes that participate in different biological effects [108]. Subsequently, complex formation of homo- and hetero-dimers of phosphorylated STAT (p-STAT) are generated, which join with interferon regulatory factors (IRF) to form different transcription factors, such as the interferon stimulated gene factor 3 (ISGF3), composed of (p-STAT1, p-STAT2 and IRF9) to schedule and control the gene expression.

Several studies have determined that cells like the cardiomyocytes have a bigger baseline expression of IFN-I when compared to CF, resulting in major nuclear baseline components activated of ISGF3 and major baseline expression of RNAm of Interferon Stimulated Gene (ISG). In contrast, the basal CF expresses more sub-units of IFNAR1 and cytoplasmic components of JAK/STAT, which allows them to be better prepared to respond to INFs [113]. In the heart, IFN-γ can also activate other non-canonical signaling pathways downstream, including protein kinase C (PKC), which may have effects on the contractile capability, as well as the remodeling of the heart [114]. In this regard, it has been demonstrated that IFN-γ regulates the phosphorylation of PKCϵ in mouse embryonic CF correlated with the responsiveness to, which may change the cell-matrix interactions [115].

3.3.2. Anti-fibrotic and anti-inflammatory effects of interferons in FC

The role played by the IFN-γ in cardiac fibrosis is controversial. Several reports remark its pro-fibrotic and anti-fibrotic effect [116]. Han et al. showed a marked decrease of α-SMA expression levels in knockout mice of IFN-γ after an infusion of Ang II, which suggest a reduced CF differentiation [117] . Likewise, KO mice of the receptor IFN-γ (IFNGR) treated with the Ang II, exhibit a decrease in cardiac hypertrophy and fibrosis, as well as a reduction in the infiltration of macrophages and T cells [118]. Savvatis et al. demonstrated that IFN-γ in rat CF led to significant decrease of the α-SMA and collagen I and III expressions, thus inhibiting the migration and differentiation of myofibroblasts [119]. (see Fig. 2).

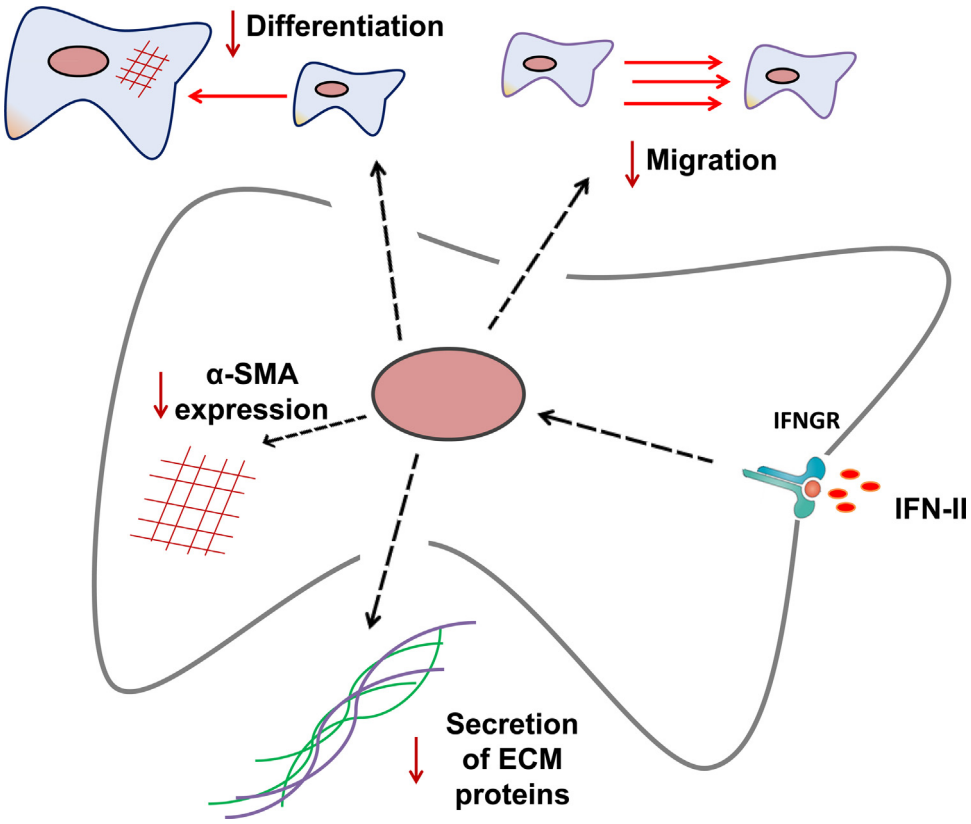

Fig. 2. Interferon receptor in cardiac fibroblasts. Interferon IFNGR is expressed in cardiac fibroblasts and its activation by IFN-II triggers cellular changes associated to cardiac fibrosis reducing α-SMA expression, collagen secretion, CF migration and CF to CMF differentiation.

Until now, there were few reports about IFN-β in CF, particularly on the study of the specific functions of formed STAT dimers. Nonetheless, in fibroblasts of different origin, it has been published that IFN-γ can induce anti-fibrotic and anti-inflammatory properties. One of these studies reported that IFN-β prevents hepatic stellate cells (HSC) activation by inhibiting signaling pathways of TGF-β and the platelet derived growth factor (PDGF), as well as a decreasing α-SMA and collagen [120], resulting in an overall reduction of the fibrotic response. Such beneficial effects have also been described in cardiac injury, where the action of the JAK/STAT pathway fulfills a protective role in the development of the cardiac remodeling of the left ventricle after a myocardial infarction. Mainly, the activation of the p-STAT3 dimers by several cytokines fulfills a cardio-protector role through the increase of angiogenesis, the decrease of inflammation, the inhibition mitochondrial, apoptosis and oxidative stress [121–123].

The inflammatory process plays a critical role in cardiac remodeling even though the activation of the inflammatory response and its specific functions in the cardiac remodeling still remain unclear. The IFN/JAK/STAT pathway may exercise control over important aspects of inflammation, ranging from leukocyte migration and invasion of tissue, their activation and effector functions [124]. Still, there are some unexplored activities of the JAK/STAT pathway, such as the regulation of the different p-STAT dimers activated by IFNs and their involvement in the production of IL-1β by the inflammasome. In this regard, IFN-I through the p-STAT1 dimer could exert suppressive activity in NLRP1 and NLRP3 inflammasomes. This has been demonstrated in a recent study which observed that IFN-I inhibits the IL-1β production through 2 different mechanisms: (a) a direct mechanism involving the suppression NLRP1 and NLRP3 inflammasomes through STAT1 activation; and (b) an indirect mechanism, inducing the expression and secretion of IL-10; which in an autocrine manner can decrease the accumulation of pro-IL-1β [125,126]. Since CF are the main producers of IL-1 β in the cardiac tissue, is seems crucial to know exactly which effects IFNs produce on CF ability to synthesize collagen and other products from the ECM, and if they stimulate the release of other fibrotic and inflammatory mediators.

4. Cardiac fibroblasts as sentinel cells: inflammatory function of fibroblasts

Increasing evidence demonstrates that cardiac tissue repair is a complex process in which the immune system has an important role in mediating the development of cardiac fibrosis [127]. Since immune and non-inmune cells coexist in the injured heart [128], it is to be expected a crosstalk between both types of cells. In this regard, a number of studies have suggested that CF are not only capable of interacting with other cardiac cells [129], but can also communicate with immune cells, such as lymphocytes, monocytes and macrophages to modulate their behavior and orchestrate heart injury and repair process [130]. It has been consistently demonstrated that CF are able to contribute to the onset, development and resolution of the inflammatory responses associated to tissue repair. At the early stages, CF are able to recruit leucocytes, via the release of chemokines including MCP-1, macrophage inflammatory protein (MIP)-1 and RANTES [131]. It has been reported that fibroblast from other tissues, such as lung or liver, directly interact with leucocytes via the leucocyte surface antigen CD40, which is expressed on fibroblasts, whereas its ligand CD40L is expressed on immune cells [132]; however, this appears not to be the case for CF as these cells do not exhibit significant levels of CD40 [133]. Nonetheless, there may be other similar interactions since CF can express adhesion molecules (ICAM-1 and VCAM-1) on their sur-

face, in response to proinflammatory stimuli [134], which suggests a possible adhesion to the immune cells attracted to the site of injury. This statement was proven by Couture et al., who reported the adhesion of neutrophils and B lymphocytes to CF [135]. These discoveries support the idea of CF as specialized immune cells recruiters, a function that was previously thought to be unique to endothelial cells. Once recruited, infiltrated leucocytes are in direct contact with cardiac cells present at the site of injury. Due to their high number and strategic location, CF appear to be of critical importance to cardiac remodeling post injury. In fact, they exhibit a wide range of phenotypical and functional alterations during the entire reparative process which allows them to modify their activity to contribute to the different phases of heart repair (from an inflammatory to an activated phenotype) [97]. It is widely known that leucocytes can modulate this phenotypic behavior of CF via the release of different inflammatory/antinflammatory cytokines, such as TGF-B1 from neutrophils or TNF-α from monocyte [133]. However, the fibroblasts can also modify the quality, quantity and duration of the inflammatory infiltrate during the induction of inflammatory responses [136]. While this statement holds true in different models of inflammatory diseases such as cancer [137], it has be to be fully proven in heart disease. In this regard, Lindner et al. described that leucocytes changed their cytokine profile activity when stimulated with conditioned medium of CF, suggesting the possible role of CF as supporter inflammatory cells in heart failure [138].

CF interaction with immune cells is not limited to their recruitment and activity during the initial events of heart repair. Buckley et al. demonstrated that they also contribute to the resolution of inflammation, by promoting the apoptosis of infiltrated leucocytes, through the tight regulation of cytokine and chemokine gradients necessary for the survival of immune cells [139]. It is interesting to hypothesize that a failure in such mechanism might be crucial in understanding how the repair process switches from an acute to chronic inflammation, since the inability of fibroblasts to eliminate the immune cells recruited during the acute phase of inflammation, would result in their accumulation in the heart tissue leading to chronic inflammation [139]. Since CF modulates all stages of leucocytes activities in the repair process (recruitment, inflammatory activity and cell death) it is probable that the maladaptive mechanism of chronic inflammation could be, partially explained by the presence of defective or over activated CF/CMF, whose cytokine secretion disrupts the normal lifespan of leucocytes infiltrated into the heart during tissue repair.

Concluding remarks

Until recently, CF were considered exclusively as supporting cardiac cells. However, in the last few years, accumulating evidence has reconsidered them as sentinel cells. The variety of receptors present on CF trigger the release of cytokines, chemokines and growth factors which enable these cells to play a key role on the inflammation and fibrotic processes. In addition, the cytokines and chemokines released by CF may affect the phenotype of surrounding cells; such as cardiomyocyte and immune cells infiltrated in infarcted area. These novel functions of CF highlight their importance in cardiac pathologies, focusing them as new interesting targets in the field of cardiovascular research.

Conflicts of interest

The authors have no conflict of interest to declare.

Statements and opinions expressed in the articles and communications herein are those of the author(s) and not necessarily those of the Editor(s), Society, or publisher, and the Editor(s), Society, and publisher disclaim any responsibility or liability for such material.

Acknowledgement

This work was supported by FONDECYT (grant 1130300 to G. Díaz-Araya).

References

[1] J.G. Meszaros, A.M. Gonzalez, Y. Endo-Mochizuki, S. Villegas, F. Villarreal, L.L. Brunton, Identification of G protein-coupled signaling pathways in cardiac fibroblasts: cross talk between G(q) and G(s), Am. J. Physiol. Cell Physiol. 278 (1) (2000) C154–C162.
[2] R.S. Ostrom, J.E. Naugle, M. Hase, C. Gregorian, J.S. Swaney, P.A. Insel, L.L. Brunton, J.G. Meszaros, Angiotensin II enhances adenylylcyclasesignalingvia Ca^{2+}/calmodulin. Gq–Gs cross-talk regulates collagen production in cardiac fibroblasts, J. Biol. Chem. 278 (27) (2003) 24461–24468.
[3] I. Olmedo, C. Muñoz, N. Guzmán, M. Catalán, R. Vivar, P. Ayala, C. Humeres, P. Aránguiz, L. García, V. Velarde, G. Díaz-Araya, EPAC expression and function in cardiac fibroblasts and myofibroblasts, Toxicol. Appl. Pharmacol. 272 (2) (2013) 414–422.
[4] R. Vivar, C. Soto, M. Copaja, F. Mateluna, P. Aranguiz, J.P. Muñoz, M. Chiong, L. Garcia, A. Letelier, W.G. Thomas, S. Lavandero, G. Díaz-Araya, Phospholipase C/proteinkinase C pathwaymediatesangiotensin II-dependent apoptosis in neonatal rat cardiac fibroblasts expressing AT1 receptor, J. Cardiovasc. Pharmacol. 52 (2) (2008) 184–190.
[5] P. Aránguiz-Urroz, J. Canales, M. Copaja, R. Troncoso, J.M. Vicencio, C. Carrillo, H. Lara, S. Lavandero, G. Díaz-Araya, Beta(2)-adrenergic receptor regulates cardiac fibroblast autophagy and collagendegradation, Biochim. Biophys. Acta 1812 (1) (2011) 23–31.
[6] P. Aránguiz-Urroz, D. Soto, A. Contreras, R. Troncoso, M. Chiong, J. Montenegro, D. Venegas, C. Smolic, P. Ayala, W.G. Thomas, S. Lavandero, G. Díaz-Araya, Differential participation of angiotensin II type 1 and 2 receptors in the regulation of cardiac cell death triggered by angiotensin II, Am. J. Hypertens. 22 (5) (2009) 569–576.
[7] M. Catalán, C. Smolic, A. Contreras, P. Ayala, I. Olmedo, M. Copaja, P. Boza, R. Vivar, Y. Avalos, S. Lavandero, V. Velarde, G. Díaz-Araya, Differential regulation of collagen secretion bykinin receptors in cardiac fibroblast and myofibroblast, Toxicol. Appl. Pharmacol. 261 (3) (2012) 300–308.
[8] A.V. Shinde, N.G. Frangogiannis, Fibroblasts in myocardial infarction: a role in inflammation and repair, J. Mol. Cell Cardiol. 70 (2014) 74–82.
[9] K.E. Porter, N.A. Turner, Cardiac fibroblasts: at the heart of myocardial remodeling, Pharmacol. Ther. 123 (2) (2009) 255–278.
[10] M. Kawaguchi, M. Takahashi, T. Hata, Y. Kashima, F. Usui, H. Morimoto, et al., Inflammasome activation of cardiac fibroblasts is essential for myocardial ischemia/reperfusion injury, Circulation 123 (6) (2011) 594–604.
[11] S. Van Linthout, K. Miteva, C. Tschöpe, Crosstalk between fibroblasts and inflammatory cells, Cardiovasc. Res. 102 (2) (2014) 258–269.
[12] W. Zhang, X. Xu, R. Kao, T. Mele, P. Kvietys, C.M. Martin, T. Rui, Cardiac fibroblasts contribute to myocardial dysfunction in mice with sepsis: the role of NLRP3 inflammasome activation, PLoS One 9 (9) (2014) e107639.
[13] O.E. Brodde, H. Bruck, K. Leineweber, Cardiac adrenoceptors: physiological and pathophysiological relevance, J. Pharmacol. Sci. 100 (2006) 323–337.
[14] S.R. Post, H.K. Hammond, P.A. Insel, Adrenergic receptors and receptor signaling in heart failure, Annu. Rev. Pharmacol. Toxicol. 39 (1999) 343–360.
[15] Ch.M. Tang, P.A. Insel, GPCR expression in the heart "New" receptors in myocytes and fibroblasts, Trends Cardiovasc. Med. 14 (2004) 94–99.
[16] M.P. Ocaranza, G. Díaz-Araya, M. Chiong, D. Muñoz, J.P. Riveros, R. Ebensperger, S. Sabat, P. Irarrázaval, J.E. Jalil, S. Lavandero, Influence of isoproterenol on the expression of angiotensin I-converting enzyme in lung, left ventricle and plasma during the development and regression of myocardial hypertrophy and fibrosis, J. Cardiovasc. Pharmacol. 40 (2002) 246–254.
[17] M.P. Ocaranza, G. Diaz-Araya, J.E. Carreno, D. Munoz, J.P. Riveros, J.E. Jalil, S. Lavandero, A polymorphism in the gene coding for angiotensin converting enzyme determines different development of myocardial fibrosis in the rat, Am. J. Physiol. Heart Circ. Physiol. 286 (2004) H498–H506.
[18] M. Copaja, R. Valenzuela, A. Saldaña, M.P. Ocaranza, J.E. Jalil, C. Vio, P. Lijnen, G.E. Ordenes, R. Vivar, S. Lavandero, G. Díaz-Araya, Early expression of monocyte chemoattractant protein-1 correlates with the onset of isoproterenol induced cardiac fibrosis in rats with distinct angiotensin-converting enzyme polymorphism, JRAAS 9 (2008) 154–162.
[19] Y. Sun, K.T. Weber, Animal models of cardiac fibrosis, Methods Mol. Med. 117 (2005) 273–290.
[20] K.T. Weber, Fibrosis in hypertensive Heart disease: focus on cardiac fibroblast, J. Hypertens. 22 (2004) 47–50.
[21] N.A. Turner, K.E. Porter, W.H. Smith, H.L. White, S.G. Ball, A.J. Balmforth, Chronic beta2-adrenergic receptor stimulation increases proliferation of human cardiac fibroblasts via an autocrine mechanism, Cardiovasc. Res. 57 (2003) 784–792.
[22] K. Iizuka, H. Sano, H. Kawaguchi, A. Kitabatake, Transforming growth factor beta-1 modulates the number of beta-adrenergic receptors in cardiac fibroblasts, J. Mol. Cell Cardiol. 26 (1994) 435–440.
[23] S.S. Roscioni, C.R. Elzinga, M. Schmidt, Epac: effectors and biological functions, Naunyn-Schmiedeberg's Arch. Pharmacol. 377 (2008) 345–357.

[24] J.L. Bos, Epac: a new cAMP target and new avenues in cAMP research, Nat. Rev. Mol. Cell Biol. 4 (2003) 733–738.
[25] G.G. Holz, G. Kang, M. Harbeck, M.W. Roe, O.G. Chepurny, Cell physiology of cAMP sensor Epac, J. Physiol. 577 (2006) 5–15.
[26] J.L. Bos, Epac proteins: multi-purpose cAMP targets, Trends Biochem. Sci. 1 (2006) 680–686.
[27] F. Colombo, J. Noël, P. Mayers, I. Mercier, A. Calderone, Beta-adrenergic stimulation of rat cardiac fibroblasts promotes protein synthesis via the activation of phosphatidylinositol 3-kinase, J. Mol. Cell Cardiol. 33 (2001) 1091–1106.
[28] J.S. Swaney, D.M. Roth, E.R. Olson, J.E. Naugle, J.G. Meszaros, P.A. Insel, Inhibition of cardiac myofibroblast formation and collagen synthesis by activation and overexpression of adenylyl cyclase, Proc. Natl. Acad. Sci. 102 (2005) 437–442.
[29] T. Mio, X.D. Liu, Y. Adachi, I. Striz, C.M. Sköld, D.J. Romberger, J.R. Spurzem, M.G. Illig, R. Ertl, S.I. Rennard, Human bronchial epithelial cells modulate collagen gel contraction by fibroblasts, Am. J. Physiol. 274 (1998) L119–L126.
[30] M. Leicht, N. Greipel, H. Zimmer, Comitogenic effect of catecholamines on rat cardiac fibroblasts in culture, Cardiovasc. Res. 48 (2000) 274–284.
[31] U. Yokoyama, H.H. Patel, N. Ch. Lai, N. Aroonsakool, D.M. Roth, P.A. Insel, The cyclic AMP effector Epac integrates pro- and anti-fibrotic signals, PNAS 105 (2008) 6386–6391.
[32] X. Liu, S.Q. Sun, A. Hassid, R.S. Ostrom, cAMP inhibits transforming growth factorbeta-stimulated collagen synthesis via inhibition of extracellular signal-regulated kinase ½ and Smad signaling in cardiac fibroblasts, Mol. Pharmacol. 70 (2006) 1992–2003.
[33] D. Grimm, M. Huber, H.C. Jabusch, M. Shakibaei, S. Fredersdorf, M. Paul, G.A. Riegger, E.P. Kromer, Extracellular matrix proteins in cardiac fibroblasts derived from rat hearts with chronic pressure overload: effects of beta-receptor blockade, J. Mol. Cell Cardiol. 33 (2001) 487–501.
[34] C.E. Pullar, C.G. Manabat-Hidalgo, R.S. Bolaji, R.R. Isseroff, β-Adrenergic receptor modulation of wound repair, Pharmacol. Res. 58 (2008) 158–164.
[35] C.E. Pullar, A. Rizzo, R.R. Isseroff, Beta-adrenergic receptor antagonists accelerate skin wound healing, JBC 281 (2006) 21225–21235.
[36] N.G. Frangogiannis, The inflammatory response in myocardial injury, repair, and remodeling, Nat. Rev. Cardiol. 11 (5) (2014) 255–265.
[37] N.G. Frangogiannis, Regulation of the inflammatory response in cardiac repair, Circ. Res. 110 (1) (2012) 159–173.
[38] A. Bürger, M. Benicke, A. Deten, H.G. Zimmer, Catecholamines stimulate interleukin-6 synthesis in rat cardiac fibroblasts, Am. J. Physiol. Heart Circ. Physiol. 281 (1) (2001) H14–H21.
[39] C. Chen, J. Du, W. Feng, Y. Song, Z. Lu, M. Xu, Z. Li, Y. Zhang, β-Adrenergic receptors stimulate interleukin-6 production through Epac-dependent activation of PKCδ/p38 MAPK signalling in neonatal mouse cardiac fibroblasts, Br. J. Pharmacol. 166 (2) (2012) 676–688.
[40] P. Timmermans, P. Benfield, A.T. Chiu, Angiotensin II receptors and functional correlates, Am. J. Hypertens. 5 (1992) 221–235.
[41] R. Zhang, Y.Y. Zhang, X.R. Huang, C-reactive protein promotes cardiac fibrosis and inflammation in angiotensin II-induced hypertensive cardiac disease, Hypertension 55 (2010) 953–960.
[42] M. De Gasparo, K.J. Catt, T. Inagami, J.W. Wright, T. Unger, International union of pharmacology. XXIII. The angiotensin II receptors, Pharmacology 52 (3) (2000) 415–472.
[43] F.J. Villarreal, N.N. Kim, G.D. Ungab, M.P. Printz, W.H. Dillmann, Identification of functional angiotensin II receptors on rat cardiac fibroblasts, Circulation 88 (6) (1993) 2849–2861.
[44] X.Q. Chen, X. Liu, Q.X. Wang, M.J. Zhang, M. Guo, Pioglitazone inhibits angiotensin II-induced atrial fibroblasts proliferation via NF-κB/TGF-β1/TRIF/TRAF6 pathway, Exp. Cell. Res. 330 (1) (2015) 43–55.
[45] Y. Ikeda, T. Nakamura, H. Takano, H. Kimura, J.E. Obata, S. Takeda, A. Hata, K. Shido, S. Mochizuki, Y. Yoshida, Angiotensin II-induced cardiomyocyte hypertrophy and cardiac fibrosis in stroke-prone spontaneously hypertensive rats, J. Lab. Clin. Med. 135 (4) (2000) 353–359.
[46] C. Warnecke, D. Kaup, U. Marienfeld, W. Poller, C. Yankah, M. Gräfe, E. Fleck, V. Regitz-Zagrosek, Adenovirus-mediated overexpression and stimulation of the human angiotensin II type 2 receptor in porcine cardiac fibroblasts does not modulate proliferation, collagen I mRNA expression and ERK1/ERK2 activity, but inhibits protein tyrosine phosphatases, J. Mol. Med. 79 (9) (2001) 510–521.
[47] S. Staufenberger, M. Jacobs, K. Brandstätter, M. Hafner, V. Regitz-Zagrosek, G. Ertl, W. Schorb, Angiotensin II type 1 receptor regulation and differential trophic effects on rat cardiac myofibroblasts after acute myocardial infarction, J. Cell. Physiol. 187 (3) (2001) 326–335.
[48] J. Bai, N. Zhang, Y. Hua, B. Wang, L. Ling, A. Ferro, B. Xu, Metformin inhibits angiotensin II-induced differentiation of cardiac fibroblasts into myofibroblasts, PLoS One 8 (9) (2013) e72120.
[49] X. Wang, J. Lu, M. Khaidakov, S. Mitra, Z. Ding, S. Raina, T. Goyal, J.L. Mehta, Aspirin suppresses cardiac fibroblast proliferation and collagen formation through downregulation of angiotensin type 1 receptor transcription, Toxicol. Appl. Pharmacol. 259 (3) (2012) 346–354.
[50] A. Whaley-Connell, J. Habibi, S.A. Cooper, V.G. Demarco, M.R. Hayden, C.S. Stump, D. Link, C.M. Ferrario, J.R. Sowers, Effect of renin inhibition and AT1R blockade on myocardial remodeling in the transgenic Ren2 rat, Am. J. Physiol. Endocrinol. Metab. 1 (3) (2008) E103–E109.
[51] M. Liu, Z. Li, G.W. Chen, Z.M. Li, L.P. Wang, J.T. Ye, H.B. Luo, P.Q. Liu, AG-690/11026014, a novel PARP-1 inhibitor, protects cardiomyocytes from Ang II-induced hypertrophy, Mol. Cell Endocrinol. 392 (1–2) (2014) 14–22.
[52] W. Zhang, X.F. Chen, Y.J. Huang, Q.Q. Chen, Y.J. Bao, W. Zhu, 2,3,4′,5-Tetrahydroxystilbene-2-*O*-β-D-glucoside inhibits angiotensin II-induced cardiac fibroblast proliferation via suppression of the reactive oxygen species-extracellular signal-regulated kinase 1/2 pathway, Clin. Exp. Pharmacol. Physiol. 39 (5) (2012) 429–437.
[53] J. Gu, X. Liu, Q.X. Wang, H.W. Tan, M. Guo, W.F. Jiang, L. Zhou, Angiotensin II increases CTGF expression via MAPKs/TGF-β1/TRAF6 pathway in atrial fibroblasts, Exp. Cell Res. 318 (16) (2012) 2105–2115.
[54] T.M. Gwathmey, E.M. Alzayadneh, K.D. Pendergrass, M.C. Chappell, Novel roles of nuclear angiotensin receptors and signaling mechanisms, Am. J. Physiol. Regul. Integr. Comp. Physiol. 302 (5) (2012) R518–R530.
[55] C.E. Squires, G.P. Escobar, J.F. Payne, R.A. Leonardi, D.K. Goshorn, N.J. Sheats, I.M. Mains, J.T. Mingoia, E.C. Flack, M.L. Lindsey, Altered fibroblast function following myocardial infarction, J. Mol. Cell. Cardiol. 39 (4) (2005) 699–707.
[56] P.A. Galie, M.W. Russell, M.V. Westfall, J.P. Stegemann, Interstitial fluid flow and cyclic strain differentially regulate cardiac fibroblast activation via AT1R and TGF-β1, Exp. Cell Res. 318 (1) (2012) 75–84.
[57] A. Leask, Potential therapeutic targets for cardiac fibrosis: TGFbeta, angiotensin, endothelin, CCN2, and PDGF, partners in fibroblast activation, Circ. Res. 106 (11) (2010) 1675–1680.
[58] M. Iwamoto, S. Hirohata, H. Ogawa, T. Ohtsuki, R. Shinohata, T. Miyoshi, F.O. Hatipoglu, S. Kusachi, K. Yamamoto, Y. Ninomiya, Connective tissue growth factor induction in a pressure-overloaded heart ameliorated by the angiotensin II type 1 receptor blocker olmesartan, Hypertens. Res. 33 (12) (2010) 1305–1311.
[59] N.L. Rosin, A. Falkenham, M.J. Sopel, T.D. Lee, J.F. Légaré, Regulation and role of connective tissue growth factor in AngII-induced myocardial fibrosis, Am. J. Pathol. 182 (3) (2013) 714–726.
[60] H. Kawano, Y.S. Do, Y. Kawano, V. Starnes, M. Barr, R.E. Law, W.A. Hsueh, Angiotensin II has multiple profibrotic effects in human cardiac fibroblasts, Circulation 101 (10) (2000) 1130–1137.
[61] J.M. Schnee, W.A. Hsueh, Angiotensin II, adhesion, and cardiac fibrosis, Cardiovasc. Res. 46 (2) (2000) 264–268.
[62] J.M. Siddesha, A.J. Valente, T. Yoshida, S.S. Sakamuri, P. Delafontaine, H. Iba, M. Noda, B. Chandrasekar, Docosahexaenoic acid reverses angiotensin II-induced RECK suppression and cardiac fibroblast migration, Cell Signal. 26 (5) (2014) 933–941.
[63] Y. Tsutsumi, H. Matsubara, N. Ohkubo, Y. Mori, Y. Nozawa, S. Murasawa, K. Kijima, K. Maruyama, H. Masaki, Y. Moriguchi, Y. Shibasaki, H. Kamihata, M. Inada, T. Iwasaka, Angiotensin II type 2 receptor is upregulated in human heart with interstitial fibrosis, and cardiac fibroblasts are the major cell type for its expression, Circ. Res. 83 (1998) 1035–1046.
[64] E.S. Jones, M.J. Black, R.E. Widdop, Angiotensin AT2 receptor contributes to cardiovascular remodelling of aged rats during chronic AT1 receptor blockade, J. Mol. Cell Cardiol. 37 (2004) 1023–1030.
[65] S. Kurisu, R. Ozono, T. Oshima, M. Kambe, T. Ishida, H. Sugino, H. Matsuura, K. Chayama, Y. Teranishi, O. Iba, K. Amano, H. Matsubara, Cardiac angiotensin II type 2 receptor activates the kinin/NO system and inhibits fibrosis, Hypertension 41 (2003) 99–107.
[66] M.P. Ocaranza, J. Moya, V. Barrientos, R. Alzamora, D. Hevia, C. Morales, M. Pinto, N. Escudero, L. García, U. Novoa, P. Ayala, G. Díaz-Araya, I. Godoy, M. Chiong, S. Lavandero, J.E. Jalil, L. Michea, Angiotensin-(1-9) reverses experimental hypertension and cardiovascular damage by inhibition of the angiotensin converting enzyme/Ang II axis, J. Hypertens. 32 (4) (2014) 771–783.
[67] J.L. Miguel-Carrasco, S. Zambrano, A.J. Blanca, A. Mate, C.M. Vázquez, Captopril reduces cardiac inflammatory markers in spontaneously hypertensive rats by inactivation of NF-kB, J. Inflamm. 7 (2010) 21.
[68] C. Duerrschmid, J. Trial, Y. Wang, M.L. Entman, S.B. Haudek, Tumor necrosis factor: a mechanistic link between angiotensin-II-Induced cardiac inflammation and fibrosis, Circ. Heart Fail. 8 (2) (2015) 352–361.
[69] H. Sato, A. Watanabe, T. Tanaka, N. Koitabashi, M. Arai, M. Kurabayashi, T. Yokoyama, Regulation of the human tumor necrosis factor-alpha promoter by angiotensin II and lipopolysaccharide in cardiac fibroblasts: different cis-acting promoter sequences and transcriptional factors, J. Mol. Cell Cardiol. 35 (10) (2003) 1197–1205.
[70] P.G. McLean, M. Perretti, A. Ahluwalia, Kinin B(1) receptors and the cardiovascular system: regulation of expression and function, Cardiovasc. Res. 48 (2000) 194–210.
[71] D.J. Campbell, The kallikrein–kinin system in humans, Clin. Exp. Pharmacol. Physiol. 28 (2001) 1060–1065.
[72] H. Yoshida, J.J. Zhang, L. Chao, J. Chao, Kallikrein gene delivery attenuates myocardial infarction and apoptosis after myocardial ischemia and reperfusion, Hypertension 35 (2000) 25–31.
[73] D. Regoli, J. Barabé, Pharmacology of bradykinin and related kinins, Pharmacol. Rev. 32 (1980) 1–46.
[74] F. Marceau, J.F. Hess, D.R. Bachvarov, The B1 receptors for kinins, Pharmacol. Rev. 50 (1998) 357–386.
[75] R. Maestri, A.F. Milia, M.B. Salis, G. Graiani, C. Lagrasta, M. Monica, D. Corradi, C. Emanueli, P. Madeddu, Cardiac hypertrophy and microvascular deficit in kinin B2 receptor knockout mice, Hypertension 41 (2003) 1151–1155.
[76] L.M. Leeb-Lundberg, F. Marceau, W. Muller-Esterl, D.J. Pettibone, B.L. Zuraw, International union of pharmacology. XLV, classification of the kinin

receptor family: from molecular mechanisms to pathophysiological consequences, Pharmacol. Rev. 57 (2005) 27–77.
[77] F. Marceau, J.F. Larrivée, E. Saint-Jacques, D.R. Bachvarov, The kinin B1 receptor: an inducible G protein coupled receptor, Can. J. Physiol. Pharmacol. 75 (1997) 725–730.
[78] C. Tschöpe, S. Heringer-Walther, T. Walther, Regulation of the kinin receptors after induction of myocardial infarction, Braz. J. Med. Biol. Res. 33 (2000) 701–708.
[79] F.J. Villarreal, T. Bahnson, N.N. Kim, Human cardiac fibroblasts and receptors for angiotensin II and bradykinin: a potential role for bradykinin in the modulation of cardiac extracellular matrix, Basic Res. Cardiol. 93 (1998) 4–7.
[80] M.E. Moreau, N. Garbacki, G. Molinaro, N.J. Brown, F. Marceau, A. Adam, The kallikrein–kinin system: current and future pharmacological targets, J. Pharmacol. Sci. 99 (2005) 6–38.
[81] V. Velarde, M.E. Ullian, T.A. Morinelli, R.K. Mayfield, A.A. Jaffa, Mechanisms of MAPK activation by bradykinin in vascular smooth muscle cells, Am. J. Physiol. 277 (1999) C253–C261.
[82] H. Ju, V.J. Venema, H. Liang, M.B. Harris, R. Zou, R.C. Venema, Bradykinin activates the Janus-activated kinase/signal transducers and activators of transcription (JAK/STAT) pathway in vascular endothelial cells: localization of JAK/STAT signaling proteins in plasmalemmal caveolae, Biochem. J. 351 (2000) 257–264.
[83] S.A. Mathis, N.L. Criscimagna, L.M. Leeb-Lundberg, B1 and B2 kinin receptors mediate distinct patterns of intracellular Ca^{2+} signaling in single cultured vascular smooth muscle cells, Mol. Pharmacol. 50 (1996) 128–139.
[84] M. Kobara, T. Tatsumi, D. Kambayashi, A. Mano, S. Yamanaka, J. Shiraishi, N. Keira, S. Matoba, J. Asayama, S. Fushiki, M. Nakagawa, Effects of ACE inhibition on myocardial apoptosis in an ischemia–reperfusion rat heart model, J. Cardiovasc. Pharmacol. 41 (2003) 880–889.
[85] M. Sato, R.M. Engelman, H. Otani, N. Maulik, J.A. Rousou, J.E. Flack, Myocardial protection by preconditioning of heart with losartan, an angiotensin II type 1-receptor blocker: implication of bradykinin-dependent and bradykinin-independent mechanisms, Circulation 102 (2000) III346–III351.
[86] A. Mailloux, B. Deslandes, M. Vaubourdolle, B. Baudin, Captopril and enalaprilat decrease antioxidant defences in human endothelial cells and are unable to protect against apoptosis, Cell Biol. Int. 27 (2003) 825–830.
[87] S. Der Sarkissian, E.L. Marchand, D. Duguay, P. Hamet, D. deBlois, Reversal of interstitial fibroblast hyperplasia via apoptosis in hypertensive rat heart withvalsartan or enalapril, Cardiovasc. Res. 7 (2003) 5775–5783.
[88] G.C. We, M.G. Siroi, R. Qu, P. Liu, J.L. Roulea, Effects of quinapril on myocardial function, ventricular remodeling and cardiac cytokine expression in congestive heart failure in the rat, Cardiovasc. Drugs Ther. 16 (2002) 29–36.
[89] A.M. Gallagher, H. Yu, M.P. Printz, Bradykinin-induced reductions in collagen gene expression involve prostacyclin, Hypertension 32 (1998) 84–88.
[90] N.N. Kim, S. Villegas, S.R. Summerour, F.J. Villarreal, Regulation of cardiac fibroblast extracellular matrix production by bradykinin and nitric oxide, J. Mol. Cell Cardiol. 31 (1999) 457–466.
[91] C. Imai, A. Okamura, J.F. Peng, Y. Kitamura, M.P. Printz, Interleukin-1beta enhanced action of kinins on extracellular matrix of spontaneous hypertensive rat cardiac fibroblasts, Clin. Exp. Hypertens. 27 (1) (2005) 59–69.
[92] M.T. Bawolak, K. Touzin, M.E. Moreau, A. Désormeaux, A. Adam, F. Marceau, Cardiovascular expression of inflammatory signaling molecules, the kinin B1 receptor and COX2, in the rabbit: effects of LPS, anti-inflammatory and anti-hypertensive drugs, Regul. Pept. 146 (2008) 157–168.
[93] Y.Z. Mozow, Z. Cuihua, Ischemia/reperfusion injury: the role of immune cells, World J. Cardiol. 2 (10) (2010) 325–332.
[94] S. Akira, Mammalian toll-like receptors, Curr. Opin. Immunol. 15 (1) (2003) 5–11.
[95] W. Chen, N.G. Frangogiannis, Fibroblasts in post-infarction inflammation and cardiac repair, Biochim. Biophys. Acta 1833 (4) (2013) 945–953.
[96] I. Sabroe, L.C. Parker, S.K. Dower, M.K. Whyte, The role of TLR activation in inflammation, J. Pathol. 214 (2) (2008) 126–135.
[97] S. Frantz, G. Ertl, J. Bauersachs, Mechanisms of disease: toll-like receptors in cardiovascular disease, Nat. Clin. Pract. Cardiovasc. Med. 4 (8) (2007) 444–454.
[98] S. Frantz, L. Kobzik, Y.D. Kim, R. Fukazawa, R. Medzhitov, R.T. Lee, R.A. Kelly, Toll4 (TLR4) expression in cardiac myocytes in normal and failing myocardium, J. Clin. Invest. 104 (3) (1999) 271–280.
[99] A. Riad, S. Jager, M. Sobirey, F. Escher, A. Yaulema-Riss, D. Westermann, A. Karatas, M.M. Heimesaat, S. Bereswill, D. Dragun, M. Pauschinger, H.P. Schultheiss, C. Tschope, Toll-like receptor-4 modulates survival by induction of left ventricular remodeling after myocardial infarction in mice, J. Immunol. 180 (10) (2008) 6954–6961.
[100] B. Dybdahl, A. Wahba, E. Lien, T.H. Flo, A. Waage, N. Qureshi, O.F. Sellevold, T. Espevik, A. Sundan, Inflammatory response after open heart surgery: release of heat-shock protein 70 and signaling through toll-like receptor-4, Circulation 105 (6) (2002) 685–690.
[101] S. Akira, K. Takeda, Toll-like receptor signaling, Nat. Rev. Immunol. 4 (7) (2004) 499–511.
[102] S. Mariathasan, D.S. Weiss, K. Newton, J. McBride, K. O'Rourke, M. Roose -Girma, et al., Cryopyrin activates the inflammasome in response to toxins and ATP, Nature 440 (7081) (2006) 228–232.
[103] F. Martinon, V. Pétrilli, A. Mayor, A. Tardivel, J. Tschopp, Gout-associated uric acid crystals activates the NALP3 inflammasome, Nature 40 (7081) (2006) 237–241.
[104] P. Duewell, H. Kono, K.J. Rayner, C.M. Sirois, G. Vladimer, F.G. Bauernfeind, et al., NLRP3 inflammasomes are required for atherogenesis and activated by cholesterol crystals, Nature 464 (7293) (2010) 1357–1361.
[105] C. Dostert, V. Pétrilli, R. Van Bruggen, C. Steele, B.T. Mossman, J. Tschopp, Innate immune activation through Nalp3 inflammasome sensing of asbestos and silica, Science 320 (5876) (2008) 674–677.
[106] Ø. Sandanger, T. Ranheim, L.E. Vinge, M. Bliksøen, K. Alfsnes, A.V. Finsen, et al., The NLRP3 inflammasome is up-regulated in cardiac fibroblasts and mediates myocardial ischaemia-reperfusion injury, Cardiovasc. Res. 99 (1) (2013) 164–174.
[107] N.A. Bracey, B. Gershkovich, J. Chun, A. Vilaysane, H.C. Meijndert, J.R. Wright, et al., Mitochondrial NLRP3 protein induces reactive oxygen species to promote Smad protein signaling and fibrosis independent from the inflammasome, J. Biol. Chem. 289 (28) (2014) 19571–19584.
[108] S.J. Noppert, K.A. Fitzgerald, P.J. Hertzog, The role of type I interferons in TLR responses, Immunol. Cell Biol. 85 (2007) 446–457.
[109] L. Ivashkiv, L. Donlin, Regulation of type I interferon responses, Immunology 14 (2014) 36–49.
[110] S.E. Applequist, et al., Variable expression of toll-like receptor in murine innate and adaptive immune cell lines, Int. Immunol. 14 (2002) 1065–1074.
[111] N.A. De Weerd, T. Nguyen, The interferons and their receptors-distribution and regulation, Immunol. Cell Biol. 90 (2012) 483–491.
[112] L.C. Platanias, Mechanisms of type-I and type-II-interferon-mediated signaling, Nat. Rev. Immunol 5 (5) (2005) 375–386.
[113] J. Zurney, K.E. Howard, B. Sherry, Basal expression levels of IFNAR and JAK-STAT components are determinants of cell-type-specific differences in cardiac antiviral responses, J. Virol. 81 (24) (2007) 13668–13680.
[114] S.F. Steinberg, Cardiac actions of protein kinase C isoforms, Physiology (Bethesda) 27 (2012) 130–139.
[115] J. Ivaska, L. Bosca, P.J. Parker, PKC epsilon is a permissive link in integrin-dependent IFN-gamma signalling that facilitates JAK phosphorylation of STAT1, Nat. Cell Biol. 5 (2003) 363–369.
[116] S.P. Levick, P.H. Goldspink, Could interferon-gamma be a therapeutic target for treating heart failure? Heart Fail. Rev. 19 (2) (2014) 227–236.
[117] Y.L. Han, Y.L. Li, L.X. Jia, J.Z. Cheng, Y.F. Qi, H.J. Zhang, et al., Reciprocal interaction between macrophages and T cells stimulates IFN-gamma and MCP-1 production in Ang II-induced cardiac inflammation and fibrosis, PLoS One 7 (2012) e35506.
[118] L. Marko, H. Kvakan, J.K. Park, F. Qadri, B. Spallek, K.J. Binger, E.P. Bowman, M. Kleinewietfeld, V. Fokuhl, R. Dechend, D.N. Muller, Interferon-gamma signaling inhibition ameliorates angiotensin II-induced cardiac damage, Hypertension 60 (2012) 1430–1436.
[119] K. Savvatis, K. Pappritz, P.M. Becher, D. Lindner, C. Zietsch, H.D. Volk, D. Westermann, H.P. Schultheiss, C. Tschöpe, Interleukin-23 deficiency leads to impaired wound healing and adverse prognosis after myocardial infarction, Circ. Heart Fail. 7 (1) (2014) 161–171.
[120] H.Y. Rao, L. Wei, J.H. Wang, R. Fei, D. Jiang, Q. Zhang, H.S. Chen, X. Cong, Inhibitory effect of human interferon-beta-1a on activated rat and human hepatic stellate cells, J. Gastroenterol. Hepatol. 25 (11) (2010) 1777–1784.
[121] P. Fischer, D. Hilfiker-Kleiner, Survival pathways in hypertrophy and heart failure: the gp130-STAT3 axis, Basic Res. Cardiol. 102 (2007) 279–297.
[122] K. Yamauchi-Takihara, gp130-Mediated pathway and heart failure, Future Cardiol. 4 (2008) 427–437.
[123] R. Bolli, B. Dawn, Y.T. Xuan, Role of the JAK-STAT pathway in protection against myocardial ischemia/reperfusion injury, Trends Cardiovasc. Med. 13 (2003) 72–79.
[124] I. Rauch, M. Müller, T. Decker, The regulation of inflammation by interferons and their STATs, JAK/STAT 2 (1) (2013), e23820.
[125] J. Tschopp, K. Schroder, NLRP3 inflammasome activation: The convergence of multiple signalling pathways on ROS production, Nat. Rev. Immunol. 10 (2010) 210–215.
[126] G. Guarda, M. Braun, F. Staehli, A. Tardivel, C. Mattmann, I. Förster, et al., Type I interferon inhibits interleukin-1 production and inflammasome activation, Immunity 34 (2011) 213–223.
[127] S. Epelman, P. Liu, D. Mann, Role of innate and adaptive immune mechanisms in cardiac injury and repair, Nat. Rev. Immunol. 15 (2015) 117–129.
[128] J. Virag, C. Murry, Myofibroblast and endothelial cell proliferation during murine myocardial infarct repair, Am. J. Pathol. 163 (2003) 2433–2440.
[129] J.E. Cartledge, C. Kane, P. Dias, M. Tesform, L. Clarke, B. Mckee, S. Al Ayoubi, A. Chester, M.H. Yacoub, P. Camelliti, C.M. Terracciano, Functional crosstalk between cardiac fibroblasts and adult cardiomyocytes by soluble mediators, Cardiovasc. Res. 105 (2015) 260–270.
[130] M. Lech, H. Anders, Macrophages and fibrosis: how resident and infiltrating mononuclear phagocytes orchestrate all phases of tissue injury and repair, Biochim. Biophys. Acta 1832 (2013) 989–997.
[131] N.W. Lukacs, S.L. Kunkel, R. Allen, H.L. Evanoff, C.L. Shaklee, J.S. Sherman, M.D. Burdick, R.M. Strieter, Stimulus and cell-specific expression of C-X-C and C–C chemokines by pulmonary stromal cell populations, Am. J. Physiol. 268 (1995) 856–861.

[132] M.J. Yellin, S. Winikoff, S.M. Fortune, D. Baum, M.K. Crow, S. Lederman, L. Chess, Ligation of CD40 on fibroblasts induces CD54 (ICAM-1) and CD106 up-regulation and IL-6 production and proliferation, J. Leukoc. Biol. 58 (1995) 209–216.
[133] Y. Seko, N. Takahashi, M. Azuma, H. Yagita, K. Okumura Yakaz, Expression of costimulatory molecule CD40 in murine heart with acute myocarditis and reduction of inflammation by treatment with anti-CD40L/B7-1 monoclonal antibodies, Circ. Res. 83 (1998) 463–469.
[134] R. Kacimi, J.S. Karliner, F. Kouddsi, C.S. Long, Expression and regulation of adhesion molecules in cardiac cells by cytokines, Circ. Res. 82 (1998) 576–586.
[135] P. Couture, J. Paradis-Massie, N.N. Oualha, G. Thibault, Adhesion and transcellular migration of neutrophils and B lymphocytes on fibroblasts, Exp. Cell. Res. 315 (2009) 2192–2206.
[136] G. Parsonage, A.D. Filer, O. Haworth, G.B. Nash, G.E. Rainger, M. Salmon, C.D. Buckley, A stromal address code defined by fibroblasts, Trends Immunol. 26 (2005) 150–156.
[137] T. Silzle, G.J. Randolph, M. Kreutz, L.A. Kunz-Schughart, The Fibroblast: sentinel cell and local immune modulator in tumor tissue, Int. J. Cancer 108 (2004) 173–180.
[138] D. Lindner, C. Zietsch, J. Tank, S. Sosalla, N. Fluschnick, S. Hinrichs, L. Maier, W. Poller, S. Blankerberg, H.P. Schultheiss, C. Tschope, D. Westermann, Cardiac fibroblasts support cardiac inflammation in heart failure, Basic Res. Cardiol. 109 (2014) 428.
[139] C.D. Buckley, D. Pilling, J.M. Lord, A.N. Akbar, D. Scheel-Toellner, M. Salmon, Fibroblasts regulate the switch from acute resolving to chronic persistent inflammation, Trends Immunol. 22 (2001) 199–204.